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THE JOURNAL OF CLINICAL ENDOCRINOLOGY

VOLUME 9 NUMBER 5

MAY 1949

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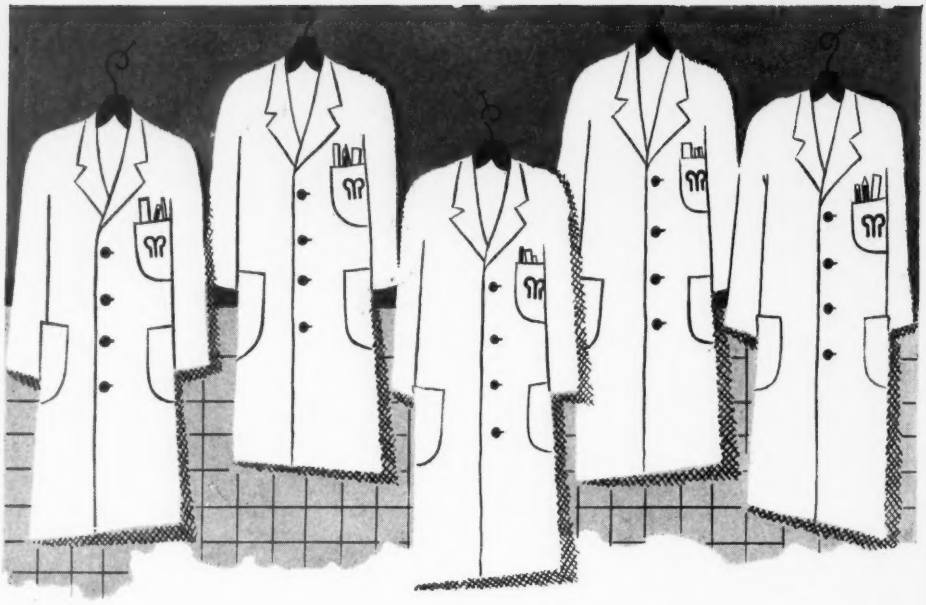
Issued monthly for The Association for the Study of Internal Secretions by Charles C Thomas, Publisher. Annual subscription, $7.50; single copies, $1.00



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VOLUME 9 MAY, 1949 NUMBER 5
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ADDISON'S DISEASE AND DIABETES MELLITUS IN THREE PATIENTS

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IN 1932 (1) the writer described a case of diabetes mellitus developing in a lad of 16 years of age with pre-existing Addison's disease. Autopsy revealed atrophy of the cortex of both adrenal glands and of the islets of Langerhans. In the present paper 2 further cases of the coexistence of Addison's disease and diabetes mellitus are recorded, one coming to autopsy; and a résumé is given of 15 other cases recorded in the literature, in which autopsies were recorded, and 6 additional cases without autopsies.

PHYSIOLOGY

Adrenalectomy results in lowering of blood sugar, particularly after starvation, and in the terminal phase death from hypoglycemia. In some species, *e.g.* marmots, other effects on carbohydrate metabolism are depletion of liver glycogen and to a lesser extent of muscle glycogen, increase of blood lactates and increase in the rate of metabolism of glucose (2, 3, 4). These effects are reversed or prevented by the administration of an adrenalin-free extract of the adrenal cortex, or by any of the 11-oxysteroids that have been isolated from the adrenal cortex, *e.g.* corticosterone, 11-dehydrocorticosterone, and 11-dehydro 17-hydroxycorticosterone (Kendall's compound E). This group of 11-oxysteroids also has a diabetogenic action as has been demonstrated in the partially depancreatized or phloridzinized rat; and the glucose-nitrogen ratio of 3.6 to 1.0 indicates that the source of the extra glucose is protein. There is also a deposition of hepatic glycogen and a depression of glucose oxidation, as shown by lowering of the

Received for publication August 25, 1948.

respiratory quotient. The 11-oxysteroids also counteract the hypoglycemic action of insulin (4, 5, 6, 7).

There is some conflict of evidence as to whether the whole of the diabetogenic action of pituitary extract is obtained by inducing hyperplasia and hyperfunction of the adrenal cortex. Houssay (8), the pioneer demonstrator of the diabetogenic action of pituitary extracts in the hypophysectomized depancreatized animal (Houssay animal) found that bilateral adrenalectomy did not prevent the diabetogenic action but hepatectomy did. Long and Lukens (9) however, found that all the significant changes in carbohydrate metabolism that occur in the Houssay animal are essentially the same as those met with in the pancreatectomized-adrenalectomized animal (Long-Lukens animal) and that the diabetogenic effects of the anterior pituitary gland were no longer obtained if both adrenal glands were completely removed. With 11-oxysteroids they could also re-establish diabetes in the adrenalectomized-pancreatectomized animal. The conflicting evidence is probably due to different species of animals being used but it seems certain that part of the diabetogenic action of pituitary extracts in mammals is mediated via the adrenal cortex (4, 9).

CASE REPORTS

Case 1. This case was described in my 1932 paper (1). The essential features were as follows: A boy stopped growing at the age of 13 and showed lassitude and weakness. At the age of 16 he presented a picture of infantilism, but pigmentation of his skin led to the correct diagnosis of Addison's disease. At this time, April 10, 1931, fasting blood sugar values were 53 mg. and 69 mg. per cent. Beginning April 18, a dose of 10 cc. of adrenal cortical extract was injected daily. Four weeks later the blood sugar reached diabetic levels of 220 mg., 250 mg., and 360 mg. per cent but the patient showed extreme sensitivity to small doses of insulin, with hypoglycemic reactions. He died on June 3, 1931, in Addisonian crisis, and autopsy showed atrophy of the suprarenals and of the pancreas. It was concluded that both pathologic lesions occurred at the same time and were of the same origin, and that the diabetes was initially obscured by the adrenal insufficiency. It would appear that the therapy with adrenal cortical extract was a factor in revealing the diabetes.

Case 2. D. C., a 37-year-old male, developed diabetes mellitus in 1921 at the age of 11, Addison's disease in 1942 at the age of 32, and died in 1947 at the age of 37 from acute adrenal insufficiency. For the first two years after the onset of the diabetes he received dietetic treatment, but in 1923 insulin was commenced. There are no quantitative details of early dosage, but it is known that in December 1941 he was receiving 36 units of soluble insulin twice daily, with a carbohydrate intake of 250 grams daily, and that during the the next few months, owing to attacks of hypoglycemia, the insulin was progressively reduced to 24 units twice daily. In spite of this apparent improvement in his carbohydrate tolerance, the patient was easily tired and did not feel well. In February, 1942, nausea and vomiting developed, in spite of a normal blood sugar and no ketosis, and about the same time some pigmentation of the face and neck appeared. He had been attending Dr. R. D. Lawrence's diabetic clinic at King's College Hospital, and was admitted as an In-Patient on March 13, 1942, in a collapsed and dehydrated state. His

blood pressure, which had previously been 120/80, was 78/50, temperature 97.6°, and respirations 22. Sugar and a trace of acetone were present in the urine, but the blood sugar was only 135 mg. per cent. A tentative diagnosis of Addison's disease was made and the patient was treated with intravenous saline and 10 cc. of adrenal cortical extract (Eucortone) every four hours and later twice daily, with the addition of 7.5 grams of salt daily by mouth. Dr. Lawrence kindly asked me to confirm the diagnosis and collaborate in the treatment of the patient. On March 14, 1942, the serum sodium was 302 mg. chloride 353 mg. and potassium 25 mg. per cent, and the alkali reserve (CO_2) was 67 volumes per cent. Apart from these blood findings and their subsequent return to normality under specific therapy, I felt that the diagnosis of Addison's disease in a diabetic could be made on the following grounds:

1. Progressive improvement in carbohydrate tolerance with recurrent hypoglycemia necessitating drastic reduction in insulin dosage; and instability of blood sugar concentration, together with hypersensitivity to insulin.
2. Weakness, wasting, nausea and vomiting, in spite of good control of the diabetes.
3. Pigmentation—although slight and not on mucous membranes.
4. Hiccups—one of a small group of accessory symptoms, the others being grimaces, curling up under the bedclothes, and conjunctivitis.

Owing to the patient's capricious appetite and his hypersensitivity to insulin, blood sugar control was very difficult in the first few weeks, insulin requirements being reduced to 12 units twice daily, with an occasional smaller dose at midday. Blood sugar on March 16 was 378 mg.; on March 30, 56 mg.; and on April 7, 1,540 mg. per cent, one of the highest values ever recorded. This was at 1 p.m. During the day, after 100 units of insulin intravenously, the blood sugar values were 917 mg. at 4:00 p.m., 495 mg. at 6:00 p.m., 61 mg. at 10:00 p.m., and 45 mg. the next morning.

Owing to the emaciated condition of the patient, the injection of large doses of cortical extract was technically difficult and painful. This was therefore replaced by desoxycorticosterone, 20 mg. injected daily. After a few days both breasts were enlarged, and painful (an occasional result of this therapy) and edema of the face and legs was present. After a very stormy course and several months in hospital, the patient was discharged reasonably well, but weak, with instructions to have injected 30 cc. of cortical extract daily, and 16 units of insulin twice daily.

The blood urea on admission was no less than 235 mg. per cent. Within a few days it fell to 140 mg. per cent, and later to 38 and 26 mg. per cent. There were no casts in the urine. The blood showed a severe secondary anemia with hemoglobin 58 per cent, red cells 2,800,000, leucocytes 9,000; polymorphs 70 per cent, lymphocytes 18.5 per cent, eosinophils 3.5 per cent, and large monocytes 8 per cent. There was a response to iron therapy. Radiography of chest, abdomen and gastro-intestinal tract showed nothing abnormal. A series of chemical studies (Dr. C. H. Gray) of serum electrolytes corresponded with the clinical condition, with occasional anomalies. Blood pressure returned to normal, 120/80.

The patient was a physician, working part-time in a biochemical laboratory and he tended to look after himself. However, he came to see me in June 1943, and stated that his diabetes was controlled by 12 units of soluble insulin twice daily, and that he was also injecting himself with cortical extract (Eschatin), 15 cc. twice daily. His general condition was fair and his blood pressure was 120/80. Serum sodium was 306, chloride 348 and urea 47 mg. per cent, and the alkali reserve (CO_2) was 52 volumes per cent. His wife, a nurse, stated that he became very ill when he tried to reduce the Eschatin to 10 cc. twice daily. In October, 1943, he replaced the Eschatin by desoxycorticosterone acetate, and found that 10 mg. injected daily, or 50 mg. rubbed into the skin daily, kept him in

good condition. On November 30, 1943, I implanted subcutaneously 600 mg. of desoxycorticosterone (6 tablets) and on December 17, 1943, he felt well. His serum sodium was 348, potassium 18.3, chloride 376, and urea 29 mg. per cent; alkali reserve (CO_2) 65 volumes per cent; blood sugar 80 mg. per cent; and B.P. 125/85. In February, 1944, he was still well. His B.P. was 140/90 and his pulse 74. Pigmentation was very slight and his weight was 120 pounds (before illness, 126 pounds). On April 5, 1944, his clinical condition was deteriorating, and he complained of weakness, nausea and hiccups. The addition of methyltestosterone, 5 mg. three times daily by mouth, had no effect. On April 26, 5 mg. of desoxycorticosterone was injected twice daily, and he immediately felt better. A few days later the serum sodium was 333, chloride 341, potassium 20, and urea 35 mg. per cent; and alkali reserve (CO_2) 61 volumes per cent. It was estimated that the implantation had been effective for some six months, and on May 26 I implanted 800 mg. of desoxycorticosterone with beneficial results. The patient was not seen for a year, but he called again on May 8, 1945. He had been well until March, 1945, when he had recommenced injections of desoxycorticosterone, 5 mg. twice daily. His insulin has been progressively reduced by himself to 2 units in the morning and 6 units in the evening, and his carbohydrate increased to 300 Gm. daily, because of recurrent hypoglycemic attacks. On May 22, 1945, I implanted 900 mg. of desoxycorticosterone acetate. There is here a gap in the notes on the attendances but on April 9, 1946, I implanted 800 mg. of desoxycorticosterone. Edema of the face developed in the next week but subsided after giving potassium citrate by mouth for a few days. On June 5, 1946, the patient was admitted to King's College Hospital under the care of Dr. Lawrence, with vomiting and malaise. His blood pressure was 140/90, temperature 105°, pulse 136, and respiration 24. His urine contained no sugar but much acetone, and his blood sugar was 120 mg. per cent. His dose of insulin was 2 units in the morning and 4 units in the evening. The blood chemistry suggested slight overdosage with desoxycorticosterone: sodium 354, potassium 15.7, chloride 350 and urea 24 mg. per cent. He was better without treatment within a few days and was discharged from the hospital.

FIG. 1. Case 2. Photograph of patient taken three weeks before death, showing characteristic degree of emaciation in spite of biochemically controlled therapy.

On November 25, 1947, I implanted 700 mg. of desoxycorticosterone and 400 mg. of testosterone, the latter because of impotence which had been present during the past few years and because of the progressive loss of weight (Fig. 1) in spite of normal blood chemistry. In the next ten days he felt much better and stronger, but on December 10 his wife noticed some puffiness around the eyes. That evening he complained of headache, weakness, shivering and perspiration. The next morning, he was incontinent and semicomatose and edema of the face was more marked. His wife then telephoned me and he was admitted to Willesden General Hospital. His pulse was hardly palpable and the blood pressure difficult to record, (?) 100/60. There were no crepitations in the lungs. He was conscious but very deaf. His blood sugar was 135 mg. per cent, and blood taken for electrolyte assay was reported a few days

later as showing the following values: sodium 321, potassium 24, chloride 398 and urea 57 mg. per cent. On December 5, five days previously, before any untoward signs were obvious the figures were sodium 324, potassium 24, chloride 332, and urea 54 mg. per cent; and alkali reserve (CO_2) 65 volumes per cent. It is difficult to understand why the potassium was not below 20 on December 11, as this is a usual finding with overdosage. However, not waiting for the result of assay, I removed on the afternoon of December 11, 300 mg. of implanted desoxycorticosterone and 200 mg. of testosterone, and during the night prescribed a total of 5 grams of potassium citrate by mouth on the basis of the clinical diagnosis of overdosage with desoxycorticosterone. It seems probable that the sodium-retaining effect of testosterone added to that of desoxycorticosterone was a factor of importance. The next morning the edema was no longer present; in fact the patient looked so dehydrated that intravenous glucose and Eucortone were commenced, but the patient died within twenty-four hours. It was incidentally noted that the eyebrows, pubic and axillary hair were very scanty. Blood sugar estimations on the afternoon of December 12, during intravenous glucose therapy, were 388 and 420 mg. per cent. The urine was sugar free and acetone free but contained albumen and granular casts.

Autopsy

Autopsy showed atrophy of the adrenals and pancreas. Apart from a small heart and a terminal bronchopneumonia, the rest of the findings were negative.

Suprarenals. The right suprarenal could not be identified macroscopically and no adrenal tissue was revealed microscopically. The left suprarenal was small, and enclosed in thick fibrous tissue. The cortical cells remaining showed almost complete absence of lipoid in the cytoplasm. There was no evidence of medullary tissue.

Pancreas. This was small, and the islet cells were diminished in numbers and small in size.

Pituitary. The basophil cells appeared to show fewer granules than normal.

Testes. Although of normal size, there was arrest of spermatogenesis at the spermatogonia stage, and some diminution in the number of interstitial cells.

Thyroid. This gland was rather small and showed some lymphoid infiltration.

Comment: case 2

This is a very exceptional case inasmuch as diabetes mellitus commenced at the age of 11, and Addison's disease did not develop until twenty-one years later at the age of 32. The treatment of both conditions was successfully maintained for a further five years and when the patient died at the age of 37, atrophy of the adrenals and of the pancreatic islet cells was found. The long period between the first appearances of the two diseases appears to preclude a common etiology. Some months before Addison's disease was obvious clinically, repeated hypoglycemic attacks necessitated progressive reduction of insulin dosage from 72 units to 48 units daily, and ultimately the daily insulin requirement was only 6 units. The patient showed the usual instability of blood sugar values when both adrenal and islet cell insufficiency were present at the same time. Some extremely high values for blood sugar were obtained, *e.g.*, 917 and 1,540 mg. per cent; and, in contrast, hypoglycemic values of 56 and 45 mg. per cent. Acetone was present at times in the urine.

The infantilism in this case must be attributed to the diabetes mellitus commencing before puberty; nevertheless the patient stated that he was potent in married life until the last few years. There was one daughter. The genitalia were on the small side, and there was appreciable loss of pubic and axillary hair and outer eyebrows. The adrenal insufficiency was treated initially by cortical extract and later by desoxycorticosterone injections and implantation. Although one implantation of 800 mg. of desoxycorticosterone and another of 900 mg. were without untoward effect, a later implantation of 800 mg. produced temporary edema and a still later implantation of 700 mg. of desoxycorticosterone and 400 mg. of testosterone resulted in excessive retention of fluids, which gave way to dehydration on the removal of 300 mg. of desoxycorticosterone and 200 mg. of testosterone and the giving of potassium citrate by mouth. The effect of testosterone on water and salt retention must be considered when this medication is added to desoxycorticosterone therapy. Ultimate death in coma was probably due to adrenal insufficiency and certainly not to diabetic coma.

Although this patient was reasonably well controlled by the administration of insulin and desoxycorticosterone there was a progressive loss of weight and strength (Fig. 1).

Case 3. L. X., a male aged 20, who was serving as an officer in the Royal Navy, was well until the age of 18½, when he began to lose weight and energy. He weighed 140 pounds at the age of 16, and 130 pounds when first seen by me in February 1947. During the preceding six months his appetite had declined further, and he felt the cold more, and in the last two months he had had frequent hiccups. Dr. S. Smith, the family doctor, had noticed some brown pigmentation on the face, and sent him to the writer as a probable case of Addison's disease. On examination he was seen to have pigmentation of the face, neck, periorbital tissue, and nipples, and slight pigmentation of the back of the hands. There was gross pigmentation of the upper gums, and a pigmented line along the lower lip. His pulse was 60, and blood pressure 120/80 at the time of examination, but 100/60 a few weeks later when lying quietly in bed at Willesden General Hospital, where he was admitted for investigation and treatment. On clinical grounds, the diagnosis of Addison's disease was definitely justified.

On February 26, 1947, the serum sodium was 302 mg., the serum potassium 31.4 mg. (very high), and the serum chloride (as NaCl) 440 mg. per cent. The blood urea was only 29 mg. per cent, and the urea clearance test showed 127 per cent of normal the first hour and 160 per cent the second hour. This test repeated a month later gave values of 116 and 110 per cent in the first and second hours. The Kepler test gave a positive result in the first procedure, the night volume of urine being 375 cc., and the largest day volume per hour, 230 cc.; but the Kepler index was 32 and higher than that given for Addison's disease, which is usually well below the upper limit of 30. Most of my cases of Addison's disease have given indices below 15, and this case is unusual in this respect. The high urea clearance test may indicate one factor in this result. The Kepler test was repeated some weeks later, after desoxycorticosterone therapy (which does not appear to change its validity), and still gave an identical index of 32. X-ray examination of the chest showed "healed lesions present in the left subapical region but no evidence of active

tuberculosis"—(D. Gordon). In this connection it is of interest to note that the patient's father died of pulmonary tuberculosis at the age of 37, and the father's sister died of abdominal tuberculosis as a child of 3. No calcification was detected radiographically in the suprarenal area, but the presumptive evidence was in favor of diagnosing a tuberculous lesion of the adrenals. Sedimentation rate was normal; 3 mm. in the first hour, and 7 mm. after two hours.

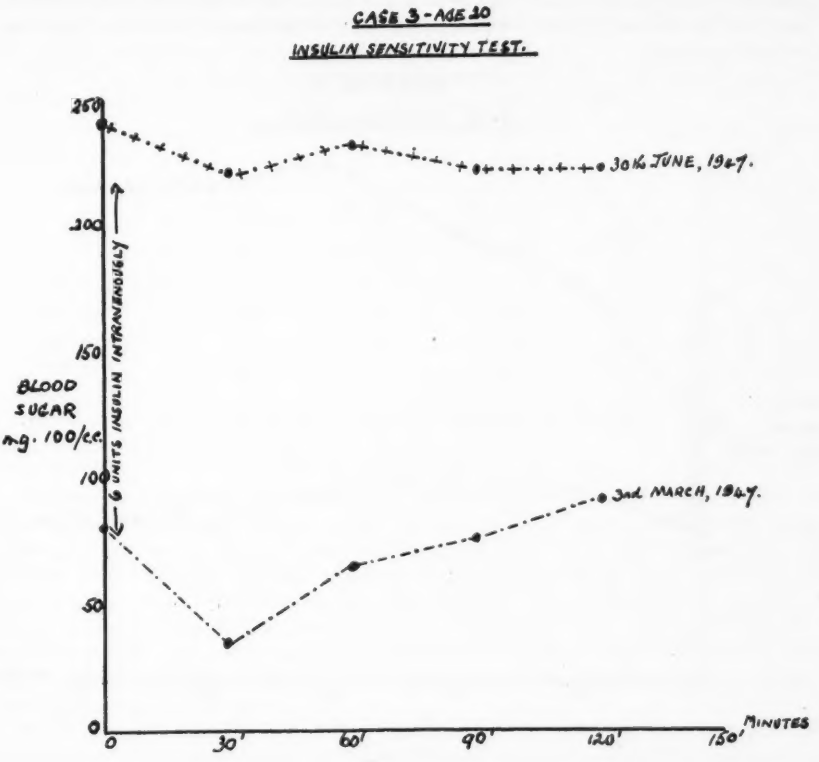

FIG. 2.

The urine was normal on routine testing. Fortunately for later developments, I was interested in carbohydrate metabolism in Addison's disease, and on February 21, 1947, a carbohydrate tolerance test was carried out and gave the following blood sugar values: fasting 115 mg.; after 50 Gm. glucose—30 minutes, 150 mg.; 60 minutes, 160 mg.; 90 minutes, 150 mg.; 120 minutes, 125 mg.; 150 minutes, 110 mg. per cent. There was a slight reduction of Fehling's solution in the urine collected after 30 minutes but not in the other specimens. This tolerance curve is not a diabetic one but values during fasting are slightly above normal and after two hours the blood sugar value is still 125 mg. per cent. However, the blood sugar (fasting) on March 3, 1947, was only 90 mg. and the insulin sensitivity test was normal (Fig. 2). The importance of these observations will be more obvious later.

On March 5, daily injections of 5 mg. desoxycorticosterone acetate were started and after a week the serum sodium was 339 mg., the serum potassium 15 mg., and the serum chloride (NaCl) 577 mg. per cent. These figures might indicate slight overdosage but the patient was very much better, gaining weight and strength and showing no edema. On March 18, therefore, I implanted 400 mg. of desoxycorticosterone. The injections of this material were stopped on March 22. The patient left the hospital on April 14, 1947, feeling very well and having gained 9 pounds in weight. The blood pressure was 120/70. There was no edema and there were no crepitations at the base of the lungs. Pigmentation had decreased.

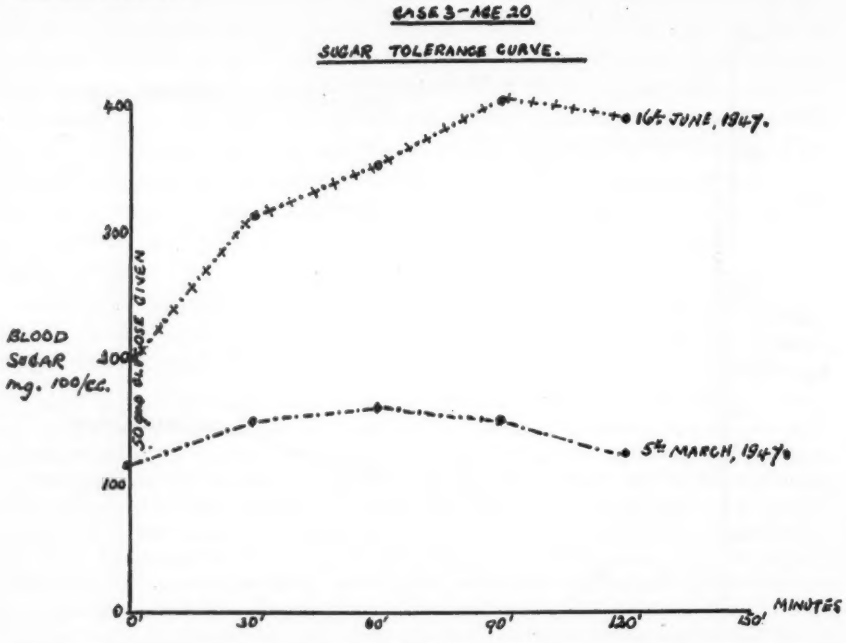

FIG. 3.

The patient continued well, except for some cramps in the arms and legs, until June 1947, when he complained of weakness, lassitude, thirst, and polyuria, and some swelling of the left parotid gland which was painful on chewing and prevented complete opening of the mouth. He had not been in contact with mumps. The thirst and lassitude appears to have preceded the swelling of the left parotid gland by some weeks. He was again admitted to the Willesden General Hospital on June 13, 1947. The urine contained sugar and acetone, both in considerable quantities. The blood sugar (fasting) was 320 mg. per cent. The blood pressure was 90/60. The swelling of the parotid gland subsided after a few days, as did a slight pyrexia, 99° F.

A carbohydrate tolerance test under the same conditions as the previous one in February 1947 gave a typical diabetic curve; fasting, 200 mg.; 30 minutes, 310 mg.; 60 minutes, 350 mg.; 90 minutes, 400 mg.; and 120 minutes, 380 mg., per cent (Fig. 3). The urine contained much sugar (red with Fehling's solution), much acetone and in the

60-minute specimen, some aceto-acetic acid. The insulin sensitivity curve was distinctly different from that of February, and indicated only a slight action of 6 units of insulin intravenously. Blood cholesterol was 130 mg. per cent. Serum sodium was 300 mg., potassium 17.9 mg., and chloride (as NaCl) 544 mg. per cent. Blood count: red cells, 4,030,000; hemoglobin 78 per cent; leucocytes 4,800; polymorphs 47, lymphocytes 49, monocytes 2, basophils 1, and eosinophils 1 per cent. A Kepler test gave an unexpected index of no less than 208, largely due to the fact that with a night volume of 425 cc. of urine, the day volumes per hour were 120, 550, 210 and 95 cc. The 17-ketosteroids (Dr. W. Payne) were 2.5 mg. per liter, and 6.4 mg. per day.

On July 3, a three-day nitrogen balance test was carried out by Dr. G. Discomb. The daily intake of nitrogen was 60 Gm. and the results were as follows:

	Urine				
	Volume cc.	Sugar Gm. %	Nitrogen Gm. %	Total sugar Gm.	Total nitrogen Gm.
1st day	2,400	2.5	0.59	60.0	14.1
2nd day	1,630	2.9	0.71	47.3	11.5
3rd day	2,930	2.6	0.55	76.2	15.2

Expected nitrogen excretion = total protein intake/6.25 = 9.58 Gm.
Mean observed nitrogen excretion = 13.6 Gm.

During the above test the diabetes was partially controlled by soluble insulin, 18 units in the morning and 16 units in the evening, and 180 Gm. of carbohydrate daily. Subsequently it was necessary to raise the dose of insulin to 28 units in the morning and 24 units in the evening, but later this was reduced to 16 units in the morning and 12 units in the evening because of hypoglycemic attacks. The patient left the hospital on July 28, 1947, with the diabetes well controlled. He felt very well and had regained a few pounds in weight lost prior to insulin therapy. His blood pressure was 100/70, and in view of the implantation of desoxycorticosterone in April, no further treatment for the adrenal insufficiency was prescribed.

He continued to remain well even in December 1947, but at that time it was felt advisable to add 1 gram of salt by mouth three times daily to the therapy, since the blood pressure was only 90/60. On January 7, 1948, he was again admitted to Willesden General Hospital following a telephone call from his mother that he had become semi-conscious several times during the last few days. He arrived thus in the hospital, the urine containing no sugar or acetone, and the blood sugar being 65 mg. per cent. The attacks were diagnosed as being due to hypoglycemia and they responded to glucose by mouth, an increase of daily carbohydrate intake from 180 to 220 Gm., and reduction of insulin to 14 units in the morning and 12 units in the evening. However, the blood sugar was somewhat unstable, values of 143, 248 and 320 mg. per cent being obtained at different times, and it was necessary subsequently to raise the insulin to 18 units and 16 units respectively.

The patient's general appearance at this time was good, but the pigmentation of the face and mucous membranes had increased. The testes and penis appeared normal but the pubic hair was somewhat scanty. The implanted desoxycorticosterone pellets

could be felt about two inches below the site of incision, and were very small. The blood pressure was 105/70. On January 16, 1948, serum sodium was 306 mg., potassium 24.5 mg. and chloride (NaCl) 676 mg. per cent (H. Scott-Wilson). The chloride was rather high, considering the low sodium and high potassium. On January 21 I implanted 300 mg. of desoxycorticosterone, and the administration of salt by mouth was stopped. On January 27 he was ill and complained of nausea. He also vomited and then refused food. He looked dehydrated. Clinically, since the diabetes was controlled and there was no evidence of edema, adrenal insufficiency was diagnosed, although the blood pressure was 110/70. He was given 10 cc. of cortical extract (Eucortone) intramuscularly, and this was repeated in four hours. He felt much better the next morning and continued well. Nausea disappeared and appetite returned. However, blood taken at the time of malaise gave little indication of the clinical diagnosis of adrenal insufficiency: sodium 309, potassium 15, and chloride 705 mg. per cent. The response to Eucortone seems to me to have justified the clinical view. The patient left the hospital on February 7, 1948, feeling very well and has so remained.

Comment: case 3

This is an undoubted case of diabetes mellitus following upon Addison's disease. It is of interest in that the lesion of the adrenals was almost certainly tuberculous, in view of the family history. It is questionable whether the parotitis was mumps, and whether it precipitated or initiated the diabetes mellitus. Mumps may be complicated by pancreatitis and transient glycosuria (Wilder, 10), but it is not established as a causative agent in diabetes mellitus. In this case it appears more probable that it aggravated a pre-existing diabetes since the blood sugar values were very high, and ketosis was present at the time of onset of the swelling of the parotid gland (only the left side was involved). It is of interest, since adrenalectomy is said to minimize ketosis, that when the diabetes was uncontrolled, ketones and acetone were present in the urine. This patient, however, could not be regarded as completely adrenalectomized.

The first procedure of the Kepler water test was positive twice before diabetes developed, and negative after diabetes developed. The index was negative throughout and grossly negative when the diabetes was severe and uncontrolled. It would appear that the Kepler index is no indication of adrenal function in the presence of diabetes mellitus.

As regards carbohydrate tolerance, the test in March 1947 suggested possibly a mild diabetes mellitus, but the test in July 1947, a very gross diabetes. The insulin sensitivity test was normal in March, but distinctly different in July, when the blood sugar showed little response. The diabetes was easily controlled by insulin, although blood sugar values were unstable and hypoglycemic attacks indicated clinically a progressive improvement in tolerance or a progressive sensitivity to insulin.

The adrenal insufficiency was controlled by desoxycorticosterone, first by injection and later by implantation, but the observed values for blood electrolytes did not always correspond to the clinical conditions.

DISCUSSION

Pathology and Etiology

In Table 1 are given some essential details of 15 cases of adrenal and islet-cell insufficiency that I have been able to trace in the literature, and of 2 cases under my own observation. Of these 15 cases, 2 (Ogle (11) and Montgomery (12)) had no evidence of Addison's disease in life. In Ogle's case the patient had pulmonary tuberculosis and "both suprarenal capsules were finely mottled with an appearance like that of the liver, and each contained a small patch of fibrinous material in the centre." In Montgomery's case the right adrenal was destroyed by caseous tuberculosis, but the left adrenal was untouched by the disease and had undergone compensatory hypertrophy. Three other cases (Rabé (13), Unverricht (14), and Bowen and associates (15) (16)), had tuberculous adrenals, so that a tuberculous lesion of the adrenal gland was present in 5 of the 17 cases. In the remaining 12, the lesion was atrophy or fibrosis of the adrenal glands.

The terms atrophy and fibrosis are used somewhat arbitrarily by different recorders, and both terms indicate the same lesion, the histologic picture of which bears a closer resemblance to a toxic necrosis (*cf.* the liver) than to a simple atrophy. There may, however, be a good deal of fibrous tissue in or around the adrenal gland and not infrequently it is almost impossible to detect any adrenal tissue macroscopically, so that the tissue in the anatomic neighborhood must be taken for section. In Nix's case (17) only one atrophied adrenal remnant could be found and that only on microscopy of regional tissue. Microscopically the cortical layer or a remnant of it is seen to be very thin, and almost entirely replaced by distended capillaries lying in a sparse, delicate, connective tissue, infiltrated with lymphocytes, plasma cells and histiocytes. Small areas of surviving and regenerating cortical cells may be detected. The medulla is usually of normal size and pattern except for some lymphocytic infiltration. In West's case (18) the adrenal lesion is correctly termed fibrosis, but there is little doubt that hemochromatosis was also present, affecting the liver. West recorded: "the notes of the autopsy have unfortunately been mislaid but so far as I remember there was nothing of importance except the condition of the suprarenal capsules. These were embedded in dense fibrous tissue, and sections showed no trace of suprarenal structure." When the lesion is tuberculous, the greater part of the adrenal gland is usually destroyed by caseous tuberculosis.

The lesion of the pancreas is also described as fibrosis or atrophy, but in the majority of cases the degree of fibrosis is slight and consists only of some increase in connective tissue. The islets of Langerhans are decreased in number, small in size, and stain poorly, and they may be hyalinized.

TABLE 1

Author	Sex	Age yrs.	Duration of diabetes before death, yrs.	Duration of Addison's disease before death, yrs.	Units of insulin required before Addison's disease	Units of insulin required after Addison's disease	Autopsy		
							Adrenals	Pancreas	Other organs—comments
1. Ogle, J. W., 1866 (11)	Male	55	<1	No clinical evidence in life	0	0	Tuberculosis.	—	Tuberculosis of lungs.
2. West, S., 1890 (18)	Male	49	<1	<1	0	0	Fibrosis.	?	Liver ++. Hemochromatosis.
3. Rabé, M., 1900 (13)	Male	49	3	?3	0	0	Tuberculosis (no pigment deposited).	Fibrosis. Hemosiderin deposited.	Liver ++. Hemochromatosis.
4. Montgomery, C. A., 1912 (12)	Male	45	1½	No clinical evidence in life.	0	0	Right: caseous tuberculosis. Left: hypertrophy. No tuberculosis.	Some increase in connective tissue; islets not abnormal.	Lungs normal. No pigmentation of skin.
5. Unverricht, 1926 (14)	Male	32	6	<1	40	10	Tuberculosis.	Not mentioned.	—
6. Arnett, J. H., 1927 (37)	Female	39	2	1½	80	20	Atrophy and fibrosis.	Slight fibrosis; islets small and poorly staining.	Acetone and diacetic acid in urine.
7. Rowntree, L. G., and Snell, A. M., 1931, Case 1 (22)	Male	35	2	1	30	?	Atrophy.	Atrophy.	Thyroidectomy but not clinically thyrotoxic.
8. Rowntree, L. G., and Snell, A. M., 1931, Case 2 (22)	Male	?	6	1	?	?	Atrophy.	Atrophy.	Footnote only. No details.
9. Gowen, W. M., 1932 (38)	Female	54	2	2	?	?	Atrophy.	Some increase in connective tissue; hyalinized islets; lymphocytic infiltration.	Not fully documented.

TABLE 1—(*continued*)

Author	Sex	Age yrs.	Duration of diabetes before death, yrs.	Duration of Addison's disease before death, yrs.	Units of insulin required before Addison's disease	Units of insulin required after Addison's disease	Autopsy		
							Adrenals	Pancreas	Other organs—comments
10. Simpson, S. L., 1932 (1)	Male	16	<1	1	0	15	Atrophy; fibrosis.	Fibrosis; small islets; lymphocytic infiltration.	Acetone but no diacetic acid in urine.
11. Rhind, E. G. G., and Wilson, A., 1941 (21)	Female	32	<1	2	0	48	Atrophy; fibrosis.	Fibrosis.	Hyperplasia of thyroid.
12. Bowen, B. D., Koepf, G. F., Bissell, G., and Hall, D., 1942 (15)	Not given	Not given	Not given	? but after diabetes	Not given	Not given	Tuberculosis.	"A small pancreas."	Description very brief.
13. Koepf, G. F., and Bowen, B. D., 1943 (39)	Female	54	2	2		<5	Atrophy.		Unpublished; brief quotation by Thorn and Clinton, 1943.
14. Nix, N. W., 1943 (17)	Male	39	<1	<1	40	?	Atrophy.	No obvious abnormality.	Acetone (trace) in urine.
15. Devitt, J. S., and Murphy, F. D., 1947 (23)	Female	28	4	1	30	10	Fibrosis.	Fibrosis; decrease in number of islet cells.	Familial diabetes.
16. Bernstein, D. E., 1948 (31)	Male	44	9	8½	56	4	Fibrosis.	Fibrosis; small islet cells with few beta cells.	Fibrous thyroid. Acetone and diacetic acid in urine.
17. Simpson, S. L., 1948 (present paper)	Male	37	26	5	72	6	Atrophy.	Small pancreas; islets small and diminished in number.	Acetone and acetodiacetic acid in urine.

There is often some lymphocytic infiltration.

Of the 11 uncomplicated cases of atrophy of adrenals and pancreas (Nos. 6, 7, 8, 9, 10, 11, 13, 14, 15, 16 and 17) in 6 of these (Nos. 6, 7, 9, 13, 14 and 16) the adrenal and islet-cell insufficiency were manifest clinically within the same year (twelve months) if not simultaneously. It is therefore my opinion (first stated Simpson (1)) that the lesion of atrophy (or fibrosis) in the adrenal gland and that of the islet cells of the pancreas have the same origin and that it is the result of some infection, probably virus in character. It is, of course, known that mumps may affect the pancreas (including the islet cells) and the testes. The probable importance of other virus infections, *e.g.* influenza, and specific fevers, in the etiology of endocrinopathies is not so well recognized, but has been pointed out by Simpson (19). The fact that clinical manifestations of Addison's disease and diabetes mellitus do not coincide in some patients does not exclude a simultaneous pathologic lesion since 1) an infective lesion may be progressive in its effects; 2) clinical insufficiency is not manifest until the greater part of an endocrine gland is destroyed, and 3) a tendency to diabetes from islet-cell insufficiency is counterbalanced by the ameliorating effect of adrenal cortex insufficiency. Thus in Thorn and Clinton's patient (20), still alive, the clinical diabetes did not develop until four years after the Addison's disease. However, a carbohydrate tolerance curve three years before the onset of the clinical diabetes, and another two years before, were diabetic in type, the later curve showing a raised blood sugar concentration as well as a slow return to normality. In my third case (patient still alive) indications of latent diabetes, as judged by the tolerance curve, were present some months prior to the onset of clinical diabetes. In my first case (number 10), although diabetes was not manifest until a few weeks before death, a year before this it was noticed that the patient drank large quantities of water and passed a great deal of urine for some weeks. It is also difficult in this case to know whether the stoppage of growth at the age of 13 and the persistent infantilism was due to the latent Addison's disease or the latent diabetes, from both of which the patient died at the age of 16. Of the remaining 4 cases (Nos. 8, 11, 15, 17) in which uncomplicated atrophy of the adrenals and of the pancreas was the lesion, that of Rhind and Wilson (21) is comparable to my first case, in that the Addison's disease appeared to precede the diabetes by some two years; in the case of Rowntree and Snell (22) and that of Devitt and Murphy (23), the diabetes preceded the Addison's disease by five and three years respectively; whereas in the case of Simpson (present paper; case 2) the diabetes preceded the Addison's disease by no less than twenty-one years. In this last case, and possibly in the 2 former ones, it would probably be conceded that the occurrence of the two diseases in one patient was a coincidence.

When the adrenal lesion is tuberculous and the pancreatic lesion atrophic, one would be justified in postulating that the two lesions were definitely separate and coincidental. However, it is perhaps necessary to remember that apart from generalized miliary tuberculosis, the pancreas is not involved in a blatant tuberculous lesion. Whether or not the tuberculous toxin can produce a fibrosis or atrophy of the islet cells of the pancreas in the absence of any local indication in the pancreas of its tuberculous origin is, of course, highly speculative.

In the metabolic disorder of hemochromatosis, hemosiderin can be deposited in the liver, spleen, pancreas, adrenals, anterior pituitary, testes, and other organs. It therefore might be expected that Addison's disease and diabetes mellitus could occur together in a patient suffering from hemochromatosis. In the present series (Table 1) there are 2 such cases, those of West (18) and Rabé (13). Unfortunately, West's is very poorly documented pathologically, the only evidence being fibrosis of the suprarenals. However, clinically the patient had definite diabetes mellitus with 56 pounds loss in weight, the liver was grossly enlarged, and the skin was of "greying cyanotic hue much like that observed in chronic silver staining." Addison's disease was thought of before death, but the clinical evidence was not strong. In Rabé's case (13) diabetes was definite, "the grey discolouration of the skin immediately made one think of Addison's disease or bronzed diabetes," the liver and spleen were grossly enlarged, and the patient died in coma. The evidence of Addison's disease in life was slender, but both adrenals were completely destroyed by caseous tuberculosis without deposition of hemosiderin. The liver showed typical hypertrophic cirrhosis with pigmentation and the pancreas "of sclerotic consistency, presented as the liver, and with a dark chocolate colour." At the apex of the right lung there was "a small nodule surrounded by fibrosis that gave the slightest suggestion of tubercle." The adrenals were "much increased in size, transformed entirely into a block of cartilaginous consistency, which recalled, after section, the aspect of tuberculous matter in a state of crudity; it was in effect a whitish amorphous substance with no pigmentation; it infiltrated completely the organ and made impossible any distinction between cortex and medulla." This case, therefore, must be considered as a coincidence of hemochromatosis affecting the pancreas and caseous tuberculosis affecting the adrenals. Achard and Leblanc (24) described a case in which the morbid anatomic findings were caseous tuberculosis of the adrenals and hemochromatosis of the liver, but there is no mention of the pancreas and no evidence of diabetes in life. There was no good clinical evidence of Addison's disease in life except pigmentation of the skin and mucous membranes, but the pathologic findings are of interest.

The specific question as to whether hemochromatosis can cause clinical Addison's disease by deposition of hemosiderin in the adrenal cortex (and in the absence of any other adrenal lesion) is not easy to answer with certainty, although it would appear to be in the negative. Thus in a statistical study of the pathology of 566 cases of Addison's disease, Gutman (25) does not mention hemochromatosis as the pathologic lesion. On the other hand Hellier (26) found than in 57 cases of hemochromatosis, hemosiderin was present in the skin in 48 and melanin in 35. In only 8 instances was hemosiderin present without melanin. Pigmentation of the mucous membranes occurred in 11 per cent of cases of hemochromatosis. If an increased deposit of melanin is taken as an indication of adrenal insufficiency, the only other manifestation of this in hemochromatosis is the not uncommon occurrence of hypotension (Sheldon (27)) but the latter might also be due to destruction of the anterior pituitary gland by hemosiderin. Although in no case in which melanin was present in excess in the skin, was iron absent from the suprarenals, iron was sometimes present without an increase of melanin. Further, melanin deposition in the adrenal gland is usually limited to the zona glomerulosa, and even there many cells escape. The increased deposition of melanin in the skin may nevertheless be due to irritation from hemosiderin deposition. Although the clinical evidence for adrenal insufficiency in hemochromatosis is not strong, and although it seems clear that the full clinical picture of Addison's disease does not result from hemosiderin deposition in the adrenals, yet some disturbance of adrenal function through hemosiderin deposition must be regarded as probable, especially as such an effect on function does result in other endocrine glands, *e.g.* pancreas, pituitary, and testis.

I have not included in this series the case of Brookfield and Corbett (28) since the adrenal lesion was very unusual, but it should be briefly mentioned. The patient was a woman of 61, who had had diabetes for six months, and was admitted to the hospital in severe diabetic coma with ketonuria and a blood sugar of 1,040 mg. per cent. (The authors mention that the highest blood sugar recorded by Joslin (29) was 1,490 mg. per cent which is less than the 1,540 mg. per cent found in my case 2.) The patient had pyrexia and leucocytosis and was refractory to insulin for some days, but then responded to large doses, *e.g.* 160 units in 24 hours, a blood sugar of 75 mg. being attained. Death occurred fourteen days later. At autopsy pancreatic islet cells showed hyaline and fibrotic changes, and both adrenals were cystic, like semicollapsed balloons. The thin shell enclosing the fluid consisted of atrophic cortical tissue, with considerable atrophy of the zona fasciculata. All organs showed congestion and fibrosis and the right kidney, multiple miliary abscesses. The authors postulated death from adrenal insufficiency although there was no evidence of Addison's disease in life.

Other endocrine glands

In Rowntree and Snell's first case (22) tachycardia was a feature, and the basal metabolic rate was plus 24 per cent. Although there is no record of the thyroid gland being enlarged, thyroidectomy was carried out, and the patient died next day in adrenal insufficiency and hypoglycemia, with a blood sugar of 50 mg. per cent. The histology of the gland showed parenchymatous hypertrophy and the case has since been repeatedly referred to in the literature as illustrating the coexistence of thyrotoxicosis together with Addison's disease and diabetes mellitus. The evidence hardly justifies the title, and it is of interest to note that in Rhind and Wilson's case (21), without any clinical evidence of thyrotoxicosis, the thyroid gland showed hyperplasia. In the other autopsy cases, where recorded, the thyroid gland was normal but with some lymphocytic infiltration. McCullagh (30) reported the coexistence of myxedema with diabetes in 5 cases; Bernstein's (31) recent autopsy report on a case previously described clinically by Bloomfield (32) illustrates myxedema and Addison's disease superimposed on diabetes mellitus, with atrophy of the thyroid, adrenals and pancreas at autopsy.

Rhind and Wilson (21) mention that "attention has been focused on the relationship between the anterior lobe of the pituitary and other endocrine glands." It is well known that the basophil cells are decreased in number and perhaps size in Addison's disease, and in Rhind and Wilson's case there was some degeneration of all three types of pituitary cells. Such changes in the pituitary gland are probably secondary, or incidental, to the adrenal and pancreatic lesions. The atrophy or cirrhosis of the adrenal glands found in the above series of cases is a distinctly different pathologic lesion from the hypoplasia or involution of the adrenal gland that follows hypophysectomy or that occurs in Simmonds' disease: nor of course are the pancreatic islet-cell changes comparable. Clinically diabetes does not occur in Simmonds' disease or panhypopituitarism. In other words, there are no grounds for postulating that the syndrome of diabetes mellitus with Addison's disease, when associated with atrophy of the adrenals and the pancreas, can be initially due to changes in the pituitary gland. Rhind and Wilson (21) point out that "the pathological changes suggest that there is no relationship between the number of basophil cells in the anterior lobe of the pituitary and the blood sugar level."

In my 1932 (1) case infantilism was present, and the testis showed "seminiferous tubules separated by much interstitial tissue in which no interstitial cells could be recognized. Few had a lumen and some of them contained spermatocytes." In my second case, impotence was present for some years, and in the testis "spermatogonia were present but spermatogenesis appeared to be arrested at a late stage. Interstitial cells of Leydig

were present, though in slightly diminished numbers." Apart from infantilism the scantiness of pubic and axillary hair met with in case 2, and to a much less extent in case 3, has also been observed by me in women with Addison's disease of some years' duration, and is probably a reflection of the low androgen secretion of the diseased adrenal cortex, as well as of hypogonadism in the case of the male.

Cases not coming to autopsy

Although this paper, including its clinical and pathological conclusions, is based on 17 cases coming to autopsy, there should be added to these for completion 6 cases without autopsy. Armstrong (33) recorded a case of a man of 35 with diabetes of acute onset, controlled by 56 units of insulin, who, within a few months of initial treatment, found it necessary to reduce progressively the dose of insulin, and within a year developed a craving for salt, severe hypoglycemic reactions from 6 units of insulin daily, and pigmentation of the skin. During the latter part of a period of five years' observation, "the most striking change has been a progressive hypothyroidism." McCullagh's case (30), a pale thin young man (? age) who had diabetes for seven years with daily insulin requirements varying between 40 and 120 units, began to complain of weakness, abdominal pains, anorexia and a loss of 30 pounds in six months. Abdominal laparotomy showed nothing abnormal but the repeated postoperative response to intravenous saline led to the diagnosis of Addison's disease. The Kepler index was positive, 6.9. Thorn and Clinton's case (20) was a man of 23 years, who developed typical Addison's disease, and who during three years of treatment with desoxycorticosterone implantations had attacks of negativism and catatonia due to hypoglycemia. He then manifested diabetes clinically and biochemically, with persistent ketonuria. His daily insulin requirements varied between 10 and 18 units. His carbohydrate tolerance curve was of the diabetic type at least two years before the onset of clinical diabetes. In the early days of treatment, the commencement of insulin therapy appeared to aggravate the tendency to low serum potassium levels, with accompanying lower limb paralysis. Withdrawal of insulin produced a striking increase in potassium excretion. The administration of a single dose of Kendall's compound E resulted in a striking decrease in glucose tolerance, a marked increase in the excretion of glucose, nitrogen, phosphorus, sodium and chloride, but not of potassium, and a decrease in the respiratory quotient.

Rogoff's case (34) of Addison's disease following adrenal denervation for diabetes mellitus in a male is not well documented but should be mentioned for completeness.

Lowrie and colleagues (35) reported this year the case of a colored

female, aged 30, who was first seen in December 1944, with emaciation, nausea and diarrhea, increased pigmentation of the skin, and new patches of pigment on the gums. The diagnosis of Addison's disease was confirmed by biochemical data, and the condition responded to desoxycorticosterone implantation. Six months later thirst and polyuria led to the discovery of sugar and acetone in the urine, and a blood sugar of 346 mg. per cent. However, the administration of 5 units of soluble insulin daily led to hypoglycemia with attacks of disorientation and even coma, which were obviated by substituting globin insulin.

My third patient (described above) remains alive and well, although in a recent temporary phase of acute adrenal insufficiency, he had a persistent hypoglycemia which nearly proved fatal.

Comment

We have seen from the previous section on pathology and etiology that clinical manifestations of adrenal and islet-cell insufficiency are not infrequently simultaneous, but that either may precede the other by some months, or occasionally years. Carbohydrate tolerance curves, when carried out, have indicated a disturbance of islet-cell function months or years before clinical diabetes manifested itself (*e.g.* Simpson's case 3; and Thorn and Clinton's case). It is perhaps more unusual for the clinical syndrome of Addison's disease to be present for some months or years before the diabetes, but this was so in 5 cases, Simpson (1), Rhind and Wilson (21), Thorn and Clinton (20), Lowrie and colleagues (35), and Simpson (case 3, present paper). In another of my cases (case 2) diabetes preceded Addison's disease by no less than twenty-one years and the two diseases coexisted for a further five years.

When adrenal insufficiency is superimposed upon a pre-existing diabetes, there is a progressive improvement in carbohydrate tolerance and a striking decrease in insulin requirements. There is also a considerable instability of blood sugar levels as if the mechanism for blood sugar regulation were missing, or impaired, and this is in keeping with the experimental evidence that the adrenal cortex, via the pituitary adrenocorticotropic hormone, plays an important part in such regulation. In my case 2, blood sugar values varied between 1,540 and 45 mg. per cent, and wide fluctuations were met with on the same day with comparatively small doses of insulin. There is usually a very considerable hypersensitivity to insulin and hypoglycemic attacks are by no means infrequent. They tend to become more frequent as the adrenal insufficiency becomes progressively worse. Nevertheless, if the diabetes is severe, insulin sensitivity with small intravenous doses of insulin may not be manifest at the time of testing (my case 3). In the case of Brookfield and Corbett (28) (*see* pathology section) severe

hyperglycemia was initially refractory to insulin, although autopsy showed cystic atrophic adrenal glands. The severity of the diabetes is aggravated by cortical extract or by members of the corticosterone group, *e.g.* Kendall's compound E. It is not thus influenced by desoxycorticosterone.

There appears to be a progressive loss of weight and fat in these patients, even when substitution therapy is approximately adequate as judged by biochemical data. The combined therapy is cumbersome and not easy to carry out although the desoxycorticosterone implantation method for Addison's disease limits the injections to insulin only, and is therefore in my view the method of choice. The tendency to ketosis appears to be diminished (as follows adrenalectomy in phloridzin diabetes), although both acetone and aceto-acetic acid may be present at times with glycosuria and hyperglycemia. Thorn and Clinton (20) suggest that ketosis is present only when dehydration is severe. This does not appear to be consistently the case in the present series, although it may well be that dehydration from adrenal insufficiency renders the patient more sensitive to ketosis and that this may be associated with anorexia and the poor intake of food. It is certainly true that death does not occur from diabetic coma, but from adrenal insufficiency or possibly from hypoglycemic coma. It is perhaps of interest to recall the case, described by Anderson (36) of a man of 33 admitted to the hospital in hypoglycemic coma without previous history, and with a blood sugar of 40 mg. per cent. He was found at autopsy to have a large left adrenal carcinomatous tumor weighing 400 grams, and a small fibrous right adrenal gland.

When testosterone is implanted, together with the desoxycorticosterone, for the treatment of an associated impotence or for its anabolic nitrogen-retaining effect, it should be remembered that it also produces a retention of sodium, so that the dose of desoxycorticosterone implanted should be lowered to allow for this. It may, however, also result in decreased potassium excretion.

Of the 3 patients under my care recorded in this paper, the first showed infantilism and the second partial infantilism. In the latter case, the diabetes commencing at the age of 11 and inadequate treatment initially, may have been the cause. In the former, it would appear that adrenal insufficiency was responsible for the infantilism. Either diabetes mellitus or Addison's disease commencing before or at puberty may be associated with infantilism, especially when adequate substitution therapy is not consistently maintained.

SUMMARY

1. Three cases of Addison's disease and diabetes mellitus are described fully with autopsy findings in the two patients who died.

2. An additional 15 recorded autopsies are summarized, making 17 in all. The islet cells of the pancreas were reduced in size and staining power, sometimes with hyalinization, and there was an increase in connective tissue and lymphocytic infiltration. The adrenal lesion was atrophy in 10 cases and tuberculosis in 3.

3. Included in the above series are two instances of hemochromatosis, in one of which the adrenal lesion was fibrosis and in the other, coincidental tuberculosis.

4. Clinically, adrenal and islet-cell insufficiency may be manifest simultaneously, or either may precede the other. When Addison's disease comes first, diabetes mellitus may be latent for months or years before it manifests itself clinically or conclusively.

5. The evidence tends to confirm the author's suggestion, first made in 1932, that the coexistence of adrenal and islet-cell atrophy may be due to a common infective lesion.

6. When adrenal insufficiency is superimposed on diabetes mellitus, there is a progressive reduction in insulin requirements, an increase in insulin sensitivity, an instability of blood sugar levels and a proneness to sudden hypoglycemia.

7. The existence, or superimposition, of adrenal insufficiency leads to a progressive loss of weight and of fat, even with reasonable substitution therapy, and ultimately death is usually due to adrenal insufficiency rather than diabetic coma.

8. The Kepler test for adrenal insufficiency is not necessarily valid in the presence of islet-cell insufficiency.

9. Insulin may accentuate the depression of the serum potassium level caused by the administration of desoxycorticosterone and salt; and inadequately controlled diabetes may have the opposite effect. Testosterone may cause a retention of potassium.

Acknowledgments

In addition to the names of colleagues mentioned under appropriate sections in the text, I wish to thank Dr. R. D. Lawrence for kindly putting at my disposal full notes on patient 2, covering the period of treatment as out-patient and in-patient at the Diabetic Department, King's College Hospital; Dr. Elizabeth Pearse for doing the microscopy in case 2; Dr. Gladys Smith for clinical pathology; Dr. Rohan Williams and Dr. Douglas Gordon for radiography; my first assistants, Dr. A. A. Lovell and Dr. Ivor Williams for help in summarizing notes in cases 2 and 3 respectively; and the Medical Research Council for a grant for assay expenses.

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THE EXCRETION OF 17-KETOSTEROIDS. I. NORMAL VALUES IN RELATION TO AGE AND SEX*

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THE purpose of the present study has been to ascertain the range and average rates of excretion of 17-ketosteroids in the urine of normal subjects at various ages as determined by the rapid method (1) previously described. Such data should prove useful for appraising results obtained in the study of endocrinopathies by the now rather large group of investigators throughout the country who have manifested an interest in, and are using the "short" method (1).

MATERIALS AND PROCEDURE

More than 450 twenty-four hour specimens of urine from 120 individuals, 93 male and 27 female, were examined. In the majority of cases three, and often many more, determinations per individual were made. More than half of the subjects were without clinical evidence of any disease. A smaller proportion were considered "normal" although they had one of a variety of disorders of a nonendocrine nature, such as pulmonary emphysema, mild anemia, coronary sclerosis, or psychoneurosis. Five cases of well-controlled diabetes mellitus were also included as we have failed to find any significant variation from normal in the excretion of 17-ketosteroids in such subjects.

Exclusive of 15 children less than 13 years old, the subjects included 85 males ranging in age from 13 to 75 years and 20 females ranging in age from 17 to 64 years. To facilitate interpretation, several arbitrary divisions according to age were made. The children were thus segregated into two groups regardless of sex, including respectively those under 5 years of age and those between 5 and 12 years old. There were 2 girls in the former and 5 in the latter group. The men were divided into four large sections according to age in years: 13 to 16, 17 to 34, 35 to 49 and 50 to 75, with 3, 53, 11 and 18 subjects respectively in each group. The second section was further subdivided into 4 age levels as follows: 17 to 19, 20 to 24, 25 to 29, and 30 to 34 years, in which there were respectively 26, 14, 10 and 3 individuals. Significant variations in relation to age were not noted in

Received for publication August 13, 1948.

* Part of a paper read by title at the Thirtieth Annual Meeting of the Association for the Study of Internal Secretions, Chicago, Illinois, June 18 and 19, 1948.

adult women; therefore, the data obtained from them have not been subjected to analysis in relation to age.

RESULTS

The daily values for urinary 17-ketosteroids for the individual subjects were averaged and the values thus obtained were used to calculate the mean and the standard deviation from the mean for each of the groups (Table 1).[1]

TABLE 1. DATA ON THE URINARY EXCRETION OF 17-KETOSTEROIDS IN NORMAL SUBJECTS (Arranged in Relation to Age and Sex)

Age group	Number of		Amount of 17-ketosteroids excreted (mg./day)			Standard deviation σ (from group means)	$\pm 2\sigma$	Coeff. of variation
	Cases	Determinations	Group average	Range of individual				
				Averages	Determinations			
Children under 5	2	3	1.4		0.7– 2.0			
5–12	13	33	3.8	2.4– 5.3	1.0– 8.2	0.9	2.0– 5.6	23.7%
Males 13–16	3	12	9.4	5.6–14.0	4.0–21.0	3.5	2.4–16.4	
17–34	53	230	18.0	11.0–27.0	9.0–30.0	3.0		16.5%
17–19	26		17.4			3.4	10.6–24.2	
20–24	14		17.8			4.0	9.8–25.8	
25–29	10		19.4			2.0	15.4–23.4	
30–34	3		20.7			1.4	17.9–23.5	
35–49	11	34	15.0	10.0–21.0	7.0–23.0	2.8	9.4–20.6	19.0%
50–75	18	60	9.0	5.0–15.0	4.0–16.0	2.6	3.8–14.2	31.0%
Females 17–64	20	100	9.3	7.0–14.0	3.0–16.0	2.0	5.3–13.3	21.5%
Totals	120	472						

Because of the difficulty in securing all the urine from the very young, only three satisfactory samples from two children under 5 years, actually $2\frac{1}{2}$ and 4 years of age respectively, were obtained. The values for 17-ketosteroids excreted in these samples were 0.7, 1.5 and 2 mg. respectively with a mean of 1.4 mg. in 24 hours. In 13 children between 5 and 12 years of age, 33

[1] We wish to thank Mr. Harold Satran, statistician to the Research Unit, for his help in carrying out the statistical calculations.

24-hour specimens were studied. Individual determinations varied from 1.0 to 8.2 mg. per day, and individual averages ranged from 2.4 to 5.3 mg. with a tendency for the older children to show the higher figures. The mean excretion for the group was 3.8 mg. daily. As compared with the younger boys, those between 13 and 16 years of age showed significantly increased values for urinary 17-ketosteroids (average, 9.4 daily) and a wide fluctuation for individual values (4 to 21 mg. daily). The averages for the individual subjects varied from 5.6 to 14 mg. per day.

As compared to other groups, men in the most active period of sexual life, 17 to 34 years, had the highest average daily output of 17-ketosteroids, *viz.* 18 mg., and the widest range of values. Averages for the individual subjects in this group varied from 11 to 27 mg. per day. Figures for individual determinations lay between 9 and 30 mg. per day. Apparently in this period of life, a direct relationship exists between age and the amount of 17-ketosteroids excreted, as the means for the four sub-groups, arranged in ascending order of age, were 17.4, 17.8, 19.4 and 20.7 mg. per day respectively.

Only a moderate decrease in the excretion of 17-ketosteroids was observed in males of 35 to 49 years of age, as compared with younger men. The average for the group was 15 mg. with a range for the averaged individual values of from 10 to 21 mg. Results of single determinations varied from 7 to 23 mg.

Results for the men, 50 to 75 years of age, and for the adult women of all ages were remarkably similar. For these two groups respectively, averages were 9 and 9.3 mg., ranges of individual averages 5 to 15 mg. and 7 to 14 mg., and variations of individual determinations from 4 to 16 mg. and 3 to 16 mg. Thus, with a decline of gonadal activity in the male the excretion of 17-ketosteroids approaches that of the female. It is perhaps significant to mention regarding the 20 females, that 6 healthy young nurses between 19 and 27 years of age excreted a daily average of 10.8 mg., in contrast to the 14 hospital female patients, 17 to 64 years old, who excreted an average of 8.8 mg. in 24 hours.

The individual averages for all men and children were plotted against age, as shown in Figure 1.[1]

For each subject the percentage average deviation of individual determinations from his mean value was obtained. In the vast majority of cases it was less than 30 per cent, and never more than 36 per cent. An overall average deviation in percentage, weighted as to the number of determinations per individual, was then calculated. This value was 17.5 per cent. The relative consistency of excretion of 17-ketosteroids from day to day for the normal person is reflected in these figures. Thus, given only a single specimen, the value generally will not deviate by more than plus or minus 30 per cent from the average which would be obtained were

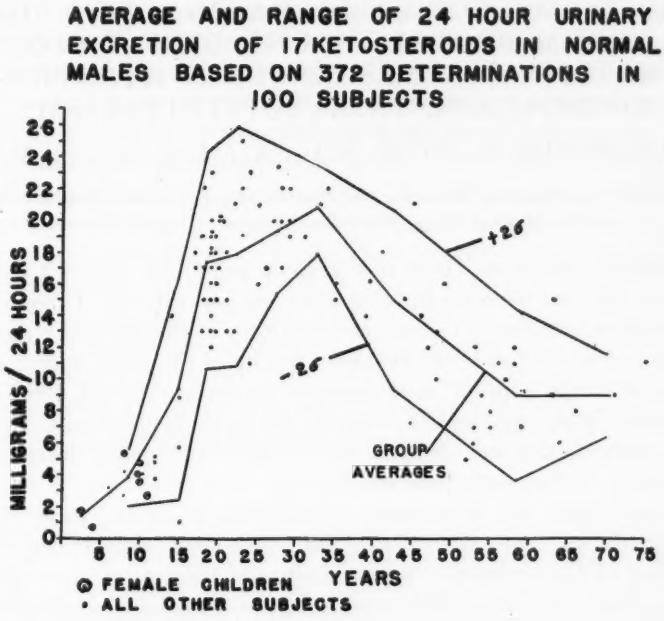

FIG. 1.

several specimens examined. In 15 subjects, the average figures for 17-ketosteroids in three consecutively collected 24-hour samples of urine varied by not more than 2 mg. from similar averages for the determinations through periods of nine days.

SUMMARY

1. The 24-hour urinary excretion of 17-ketosteroids for each of 120 normal subjects, 93 male and 27 female, was determined by a rapid method to establish mean values in relation to age and sex.

2. The average daily excretions of 17-ketosteroids for children, under 5 and between 5 and 12 years of age were 1.4 and 3.8 mg., respectively. For 4 groups of males arranged according to age (13 to 16; 17 to 34; 35 to 49; and 50 to 75 years), the corresponding values were 9.4, 18.0, 15 and 9.0 mg., respectively. The average excretion for females was 9.3 mg.

3. By plotting the individual averages of children and adult males against age, a graph has been constructed which gives the mean and range of the mean 24-hour urinary excretion of 17-ketosteroids.

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THYROID COLLECTION OF RADIOACTIVE IODIDE AND SERUM PROTEIN-BOUND IODINE CONCENTRATION IN SENESCENCE, IN HYPOTHYROIDISM AND IN HYPOPITUITARISM*

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IN normal senescence, there is a gradual reduction in basal metabolic rate as well as a decrease in basal body temperature (1). These phenomena have been attributed to decreased activity of the thyroid gland in the aged. Anatomic studies have revealed atrophy of the acini, decrease in the colloid and iodine content, and decrease in the number of dividing cells in the senile gland as compared to the gland of young adults (2). Thus there is both clinical and morphologic evidence to suggest decreased thyroid activity in the senile individual.

Although there has been much speculation as to the cause of senile "hypothyroidism," no experimental data have been presented to elucidate this aspect of the problem. Primary failure of the thyroid to supply adequate hormone has been considered to be the cause of this hypometabolic state (2, 3). Others have postulated that pituitary hypofunction is the primary cause (1).

Benedict's (4) and Boothby's (5) classic studies, thirty years ago, demonstrated that the basal metabolic rate was a useful clinical gauge of thyroid activity. Within the past decade, two more direct assays of thyroid function have been developed, *i.e.* the chemical determination of the concentration of protein-bound iodine in the serum and the determination of the rate of accumulation of radioactive iodide by the thyroid. Salter, Bassett and Sappington (6) and Winkler and associates (7) have demonstrated the very close correlation between the concentration of serum protein-bound iodine and the clinical estimation of thyroid activity. The protein-bound iodine may usually be considered an index of the circulating thyroid hormone. Hamilton and Soley (8) and Hertz and co-workers (9) have shown that the rate of accumulation of radioactive iodide by the

Received for publication August 7, 1948.

Read by title at the Thirtieth Annual Meeting of the Association for the Study of Internal Secretions, Chicago, Illinois, June 18 and 19, 1948.

* This study was aided in part by a grant to Dr. G. W. Thorn from the Committee on Research in Endocrinology, National Research Council, and in part by a grant from Armour Laboratories to the Harvard Medical School.

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thyroid can be measured with an externally placed Geiger-Müller counter. Since Morton and associates (10) have demonstrated that most of the iodide accumulated in the normal thyroid is rapidly converted into organically bound iodine, the rate of iodide accumulation by the thyroid can usually be considered indicative of the rate of thyroid hormone synthesis.

Utilizing these two newer methods, the rate of thyroid hormone synthesis and the concentration of circulating thyroid hormone were studied in senescence, in primary hypothyroidism, and in primary hypopituitarism. The rate of radioactive iodide accumulation by the thyroid was determined in 160 hospitalized patients with presumably normal thyroid function, and in 13 patients with hypothyroidism or hypopituitarism. Determinations of the serum concentration of protein-bound iodine were limited to the sera of untreated hypothyroid or hypopituitary patients and of 17 patients clinically free of hypothyroidism or hyperthyroidism, many of whom exhibited a sluggish rate of iodide uptake.

METHODS

The euthyroid subjects were hospitalized patients whose illness had no apparent effect upon their thyroid function; clinically, these patients demonstrated no evidence of thyroid dysfunction. In the others, the diagnosis of hypothyroidism or hypopituitarism was made on clinical grounds. Three hypopituitary patients and one probable hypothyroid patient were kindly sent to us by Dr. F. Albright for this study.

The radioactive iodide, I^{131}, was obtained from the Clinton Laboratories, Oak Ridge, Tennessee. The half-life of this isotope is eight days.

The rate of uptake of radioactive iodide was determined by the method of Stanley and Astwood (11). One-tenth of a millicurie of carrier-free radioactive iodide in approximately 50 ml. of water was administered orally about thirty minutes before breakfast or luncheon. The radioactive iodide was contained in approximately 50 ml. of water. A second 50 ml. of water was taken immediately after the first in order to rinse the radioactive isotope from the glass, mouth, and esophagus. A Geiger-Müller tube, without a lead shield, was placed against the neck as described by Stanley and Astwood (11). A brass shield was placed over the window of the Geiger-Müller tube to block beta radiation from the sweat. Counts, in duplicate, of the gamma radiation emanating from the neck were taken at 1, 2, 3, and 4-hour intervals after the ingestion of the radioactive isotope. The counts per second were plotted as the ordinate and the square root of the time as the abscissa. The slope of this line, approximating a straight line in almost every case, is a numerical expression of the rate of accumulation of iodide by the thyroid and has been termed the *accumulation gradient* by Stanley and Astwood (11). A positive gradient indicates increasing

iodide uptake by the thyroid. A negative gradient signifies that the initial count at one hour after ingestion of iodide was the greatest and that the count decreased during the ensuing three hours.

The protein-bound iodine[1] of the serum was assayed according to the method of Man and associates (12).

RESULTS

In euthyroidism: The individual accumulation gradients of over 160 patients, who clinically demonstrated no evidence of thyroid dysfunction, are grouped in Tables 1 and 2, according to sex and age. Because there was

TABLE 1. ACCUMULATION GRADIENTS OF EUTHYROID MEN.

Age in years	12–19	20–29	30–39	40–49	50–59	60–69	70 and over
	4.2	6.4	3.4	4.5	2.1	2.9	0.4
	4.8	4.5	2.4	2.3	1.8	1.3	0.4
	3.9	7.4	3.7	1.9	3.7	1.9	0.5
	3.1	3.9	3.4	2.7	3.4	2.3	1.2
	4.0	2.3	2.5	1.6	1.0	3.0	
	10.2	4.5	2.2	11.0	3.6	2.8	
	9.7	1.4	2.2	4.1	2.8	1.2	
	5.5	3.1		2.2	1.2	0.7	
	1.7	2.8		2.6	0.6	1.5	
	0.0	1.2		1.3	1.9	0.7	
	1.7	3.8		3.5	0.6	1.2	
		4.2		3.0	1.6		
		1.4		−0.4			
				0.7			
Mean	4.4	3.8	2.8	2.9	2.0	1.8	0.6
S.E.M.*	0.95	0.53	0.08	0.71	0.31	0.23	0.2

* Standard error of the mean.

considerable scatter within each group and because the number of patients in the seven sub-groups was small, the series was divided into three larger groups. The pubertal group ranged in age from 12–19 years, the young adult group from 20–49, and the elderly adult group, from 50 years up. In Tables 3 and 4, the mean gradients of these three groups are compared.

The effect of aging upon the mean accumulation gradient is presented in Table 3. In both the male and female series, the mean gradients of the

[1] The following ranges are given as a guide to the interpretation of serum protein-bound iodine values: 0–2.9 gamma %, subnormal; 3.0–3.4 gamma %, borderline low; 3.5–6.9 gamma %, normal; 7.0–7.9 gamma %, borderline high; above 8.0 gamma %, above normal.

young adult groups are, statistically, significantly higher than those of the older group.

The difference in gradients between the two sexes is summarized in Table 4. There is no apparent difference between the rate of iodide uptake by the thyroid of the adolescent male and that of the adolescent female in this small series. In contrast, the mean gradient of the females is higher than

TABLE 2. ACCUMULATION GRADIENTS OF EUTHYROID WOMEN.

Age in years	12–19	20–29	30–39	40–49	50–59	60–69	70 and over
	3.2	4.8	5.2	5.1	2.8	3.0	1.6
	6.0	9.7	3.9	5.6	6.3	1.3	2.7
	4.5	4.2	1.5	2.4	1.8	1.7	1.0
	5.0	3.3	2.6	5.1	2.1	1.3	3.3
	1.6	4.2	3.7	5.4	6.6	2.0	2.9
	4.1	8.4	0.6	6.3	5.2	3.1	1.4
		4.5	8.4	7.8	4.9	1.1	1.4
		6.3	10.7	2.8	3.6	1.1	2.4
		5.0	4.4	11.9	1.2	0.9	4.6
		1.8	2.5	1.6	0.0	0.9	
		3.3		9.4	1.8	0.4	
		1.3		1.6	1.8	1.0	
		3.8			0.9	4.8	
					0.7	3.6	
					1.9	2.3	
					1.6	3.0	
					2.9	2.9	
					1.5	5.8	
					1.1	3.1	
					1.6	0.5	
Mean	4.1	4.7	4.4	5.4	2.5	2.2	2.4
S.E.M.*	0.62	0.65	0.95	0.95	0.42	0.33	0.38

* Standard error of the mean.

the corresponding mean of the males in both the young adult and the older adult groups. These differences are probably significant, statistically, since the t values are over 2.

As mentioned above, the protein-bound iodine assays were made on the sera of only 17 of the apparently euthyroid individuals. The ages, accumulation gradients and protein-bound iodine concentrations of these patients are presented in Table 5. With one exception, the concentrations of the serum protein-bound iodine were normal despite the low gradients of most of these patients.

TABLE 3. MEAN ACCUMULATION GRADIENTS IN YOUNG AND ELDERLY ADULTS. EFFECT OF AGING.

	Mean ±S.E.M.	No. in series	Mean ±S.E.M.	No. in series	Difference of means ±S.E.M.	*t* Value	Per cent chance that difference is significant
Age in years	20–49		50 and over				
Females	4.8 ±0.47	35	2.4 ±0.22	49	2.4 ±0.51	4.6	99.99
Males	3.2 ±0.36	34	1.7 ±0.19	27	1.5 ±0.43	3.5	99.95

TABLE 4. DIFFERENCE OF MEAN ACCUMULATION GRADIENTS IN MALES AND FEMALES.

	Mean ±S.E.M.	No. in series	Mean ±S.E.M.	No. in series	Difference of means ±S.E.M.	*t* Value	Per cent chance that difference is significant
Sex	Females		Males				
Age: 12–19	4.1 ±0.62	6	4.4 ±0.95	11	0.3 ±1.1		
20–49	4.8 ±0.47	35	3.2 ±0.36	34	1.6 ±0.59	2.7	99.31
50 and over	2.4 ±0.22	49	1.7 ±0.19	27	0.7 ±0.29	2.4	98.36

In hypothyroidism and hypopituitarism: Eight myxedematous patients were included in this study. Three of these patients had received no thyroid therapy for more than one month prior to the determination of the rate of iodide uptake by their thyroids. Maintenance thyroid medication had not been discontinued in the other 5 patients. The ages, sex, protein-bound iodine concentrations, and accumulation gradients are presented in Table 6.

The radioactive iodide uptake of 5 patients with hypopituitarism was studied; the serum concentration of protein-bound iodine was determined in 3 of these patients. The ages, sex, protein-bound iodine concentrations, and accumulation gradients are presented in Table 7.

DISCUSSION

Technique: Our data agree with Stanley's reports (11, 13) that the accumulation of radioactive iodide by the thyroid approximates a straight line, when the counts per second are plotted against the square root of the time since the ingestion of the isotope. Our accumulation gradients for apparently normal individuals ranged from 0 to 12. This is in close agree-

TABLE 5. ACCUMULATION GRADIENTS AND SERUM PROTEIN-BOUND IODINE CONCENTRATIONS OF EUTHYROID PATIENTS.

Sex	Age (yrs.)	Gradient	Serum protein-bound iodine (gamma %)
F	28	9.7	5.0
F	38	8.4	5.6
F	38	0.6	4.1
F	38	1.5	3.8
M	40	1.9	6.4
M	43	1.3	4.0
M	60	2.9	3.6
F	61	1.3	5.0
F	63	0.4	4.1
F	63	1.1	4.2
M	64	1.2	5.3
F	65	1.7	6.1
M	66	1.9	2.4*
F	66	0.9	4.6
M	69	0.8	5.1
F	69	3.0	4.8
F	70	5.5	4.5

* This patient had central nervous system syphilis and clinically did not appear to be hypothyroid.

ment with Stanley's report (13) that the normal range was between 1 and 15.

It would be well to point out that falsely low gradients may be caused by the antecedent ingestion or injection of compounds containing inor-

TABLE 6. ACCUMULATION GRADIENTS AND SERUM PROTEIN-BOUND IODINE CONCENTRATIONS OF PATIENTS WITH HYPOTHYROIDISM

Sex	Age (yrs.)	Serum protein-bound iodine (gamma %)	Concurrent thyroid therapy	Accumulation gradient
F	38	0.8	0	0.5
M	40	—	0	−0.1
F	48	—	0	−0.5
F	49	—	+	0.6
M	56	—	+	−0.1
F	50	—	+	−0.3
F	78	—	+	−0.3
F	59	0.3	+	−0.5

ganic or organic iodine. The iodides commonly used as medication, and those iodine-containing compounds used in x-ray examinations of the kidney, lungs, and gallbladder, flood the thyroid with iodide so that falsely low gradients are obtained. Antecedent or concurrent thyroid therapy lowered the gradient in two of our euthyroid patients from 1.6 to 0.5 and from 4.2 to 2.2 respectively. To date, no falsely high rates have been recognized. It is considered likely that some of the low gradients in this series may have been due to undetected antecedent iodide ingestion.

Aging: Our data indicate that there is a decreased rate of iodide uptake in senescence (presumably indicating a decreased rate of thyroxin forma-

TABLE 7. ACCUMULATION GRADIENTS AND SERUM PROTEIN-BOUND IODINE CONCENTRATIONS OF PATIENTS WITH HYPOPITUITARISM

Sex	Age (yrs.)	Serum protein bound iodine (gamma %)	Concurrent thyroid therapy	Accumulation gradient
F	43	—	0	0.7
M	47	1.9	0	1.3
M	47	2.7	+	0.1
F	38	—	+	0.3
F	28	2.3	+	1.4

tion); however, this is associated with a normal level of circulating thyroid hormone. The normal level of blood protein-bound iodine indicates that there is no diminution in the concentration of thyroid hormone reaching the tissues. This suggests that the low rate of thyroid hormone production in senescence is not due to thyroid hypofunction, either primary or secondary to pituitary failure.

It has been demonstrated experimentally that thyroxin administration decreases the thyrotropic hormone (T.S.H.) content of the rat's pituitary to less than 5 per cent of the normal value (14). It has also been demonstrated that administration of thyroid to the normal human temporarily causes thyroid hypofunction (15). As noted here, thyroid medication did lower the gradient in two of our patients. It seems probable that a high level of circulating thyroid hormone depresses T.S.H. production and secretion. That thyroid activity is in large part directly controlled by the pituitary T.S.H. has been well documented. Thus it seems that the concentration of the circulating thyroid hormone indirectly controls the activity of the thyroid. The concentration of the thyroid hormone in the blood depends not only upon the rate of secretion from the thyroid, but also upon the rate of utilization by the tissues or excretion from the body. Decreased utilization of the thyroid hormone by the peripheral tissue

might tend to elevate temporarily the concentration of circulating hormone. This presumed temporary elevation of the concentration of circulating thyroid hormone might depress T.S.H. production and thus decrease thyroid activity. This lowered thyroid hormone synthesis would result in decrease of the temporarily elevated circulating hormone level to normal. Thus a normal circulating hormone concentration may be maintained when there is a decrease in the peripheral utilization of thyroid hormone, by means of decrease in thyroid activity. It is suggested that the thyroid hypofunction of senescence may be caused by such a postulated homeostatic mechanism of maintaining a normal level of circulating hormone. This agrees with Thewlis' (1) conclusion that the thyroid atrophy of senescence is not associated with pituitary hypoplasia and is probably due to decreased requirement of the end organ.

Thyroid function may thus be under the control of its end organ, the peripheral tissue, as well as being under the control of its master gland, the pituitary. Sayers and Sayers (16) have postulated a similar control of adrenal cortical function by the peripheral tissue and the pituitary.

If this theory is true, it would indicate that the senile patient with myxedema might need less thyroid replacement therapy than do younger hypothyroid patients. Mueller-Deham and Robson (17) have reported that in the senile hypothyroid patient, the effective dose of thyroid extract is usually smaller than in earlier age groups.

Sex differences: Hyperthyroidism has long been recognized as predominantly a disease of women. It is therefore of interest to note that, after puberty, the rate of radioactive iodide uptake is greater in the female than in the male. It is possible that the more active thyroid gland during the adult female's active sex life is associated with increased peripheral utilization of the thyroid hormone in the presence of the sex hormones. It has been demonstrated that the basal metabolic rate of the hypopituitary individual may be raised by testosterone therapy alone (18). Perhaps the sex hormones, by speeding up body metabolism, may increase the peripheral utilization of thyroxin. The sharp fall of the mean accumulation gradient after the menopause in the female is consistent with this theory. Studies of the effect of sex hormones upon the accumulation gradient are contemplated in order to test this theory.

Hypothyroidism and hypopituitarism: The gradients were low in every case of hypothyroidism and in 4 of the 5 cases of hypopituitarism; it was normal in the fifth hypopituitary patient. Although the gradients seem to be lower in the untreated hypothyroid patients than in the untreated hypopituitary patients, more data are necessary before any conclusion can be reached as to their value in the differential diagnosis of these two conditions. The serum protein-bound iodine levels were definitely below normal

in these cases. Sheehan's (19) pathologic studies in cases of pituitary failure indicate only partial thyroid atrophy in this condition. Thus one would expect that thyroid function would be decreased less in hypopituitarism than in hypothyroidism.

Value of tests: The combined use of the rate of uptake of radioactive iodide and the assay of circulating protein-bound iodine has made possible a dynamic study of thyroid physiology in senescence and in certain hypometabolic states which would have been impossible without these tools. Further combined use of these tests should help to define the role of aberrations of thyroid function in other syndromes associated with abnormal metabolism.

The rather wide scatter of the gradients within each subgroup in Tables 1 and 2 emphasizes the impracticability of using the gradient as the sole means of diagnosing thyroid abnormality. However, when used in conjunction with the assay of circulating protein-bound iodine, it is a test of physiologic as well as of diagnostic importance.

SUMMARY

A study has been made of the rate of uptake of radioactive iodide by the thyroids of 160 apparently euthyroid and 13 hypothyroid or hypopituitary patients. The level of protein-bound iodine of the serum was determined in selected cases.

The causes of a low rate of iodide uptake are discussed. There is considerable scatter of the uptakes within the euthyroid groups.

The mean accumulation gradient, a measure of the rate of iodide uptake, decreases with aging. This decreased gradient is not associated with a decreased concentration of circulating protein-bound iodine.

In the male, there is a gradual drop in the mean gradient from puberty to senescence. In the female there is a sharp drop in the mean gradient, after the menopause, to low levels. There is no sex difference in the mean gradients at puberty; however, after puberty, the mean gradients in the female are consistently higher than in the male.

The accumulation gradients tend to be low in hypothyroidism and in hypopituitarism; in these diseases, they are associated with a subnormal concentration of serum protein-bound iodine.

A mechanism, whereby the peripheral tissue may regulate thyroid function, is postulated and the possible influence of the sex hormones upon peripheral utilization of the thyroid hormone is discussed. Our data suggest that the decreased activity of the thyroid gland in senescence is primarily associated with decreased peripheral utilization of the hormone.

The combined use of the rate of uptake of radioactive iodide and the assay of the circulating protein-bound iodine offers a valuable method for the study of abnormal metabolic states.

Acknowledgment

The authors wish to thank Dr. G. W. Thorn for his many helpful suggestions. They are indebted to Dr. P. H. Forsham for his aid in the preparation of this manuscript.

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DECREASES IN BLOOD EOSINOPHILIC LEUKOCYTES AFTER ELECTRICALLY INDUCED CONVULSIONS IN MAN

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THE data of earlier work (1, 2, 3, 4, 5, 6) indicate the occurrence of strong stimulation of the adrenal cortex during and after convulsions induced electrically in the treatment of mental disease. The possible importance of increased secretion of some steroid hormones in causing the beneficial response to electroconvulsive therapy is suggested by clinical studies on the effects of testosterone in large doses in patients in relapse after having recovered from mental disease as a consequence of shock therapy (7).

The steroid hormones are known to have several different functions. In an attempt to gain insight into which of these functions might be important in relation to the beneficial effects of shock therapy, it was decided to study the blood eosinophil count in patients given this form of treatment.

MATERIAL AND METHODS

Twenty-one patients, ranging in age from 22 to 65 years, were studied; 14 were women. The diagnoses were various (Table 1). Some of the patients had been ill for long periods but none was more than slightly deteriorated. In the case of the patients with schizophrenia, the clinical course was variable but none of the patients was entirely well for any prolonged period. The patients with manic-depressive psychoses, on the other hand, had periods of complete normality of some duration; in these instances the duration of the present attack is indicated in parentheses in Table 1.

The method described by Forsham and associates (8) was used. A sample of venous blood was taken immediately before a convulsion was induced and again four, eight and, in a few instances, twenty-four hours later. The schedule of treatments was determined by clinical considerations. Forty-six experiments were performed; an additional study was made on one subject who also was given adrenocorticotropic hormones.

OBSERVATIONS

The eosinophil counts were within the normal range before shock in all instances but one; one patient (Case 6) had an unexplained eosinophilia of 11 per cent so that his eosinophilic cells numbered 2000 per cu.mm. of

TABLE 1

Case No.	Age yrs.	Sex	Diagnosis	Total duration	Per cent decrease in eosinophils			Number of shock treatments	Schedule of shock treatments
					in 4 hours	in 8 hours	in 24 hours		
1	57	F	Schizophrenia, paranoid	25 years	100 100 91	100 — —	88 — —	1 10 14	Nine, given three times weekly: a rest of 22 days, then three times weekly.
2	47	M	Schizophrenia, catatonic	6 months	94 50	62 25	— —	1 18	Three times weekly.
3	22	F	Schizophrenia, catatonic	2 years	75 48	0 0	38 —	2 5	Three times weekly.
4	31	M	Schizophrenia, hebephrenic	8 years	75 24 75 64	50 0 — —	— — — —	6 7 11 13	Seven, given once weekly; a rest of 11 days, then three times weekly.
5	30	F	Schizophrenia, catatonic	9 years	45 0	8 0	0 —	6 28	Six, given three times weekly. Then 20, twice weekly.
6	30	M	Schizophrenia, hebephrenic	14 years	0	60	49	11	Three times weekly.
7	36	F	Schizophrenia, paranoid	18 months	83 79	52 —	— —	16 17	Ten, given three times weekly; then one, every 2–3 weeks.
8	50	F	Schizophrenia, paranoid	6 years	18 40	0 11	0 40	27 32	One every five days.
9	25	F	Schizophrenia, paranoid	18 months	77 33	50 0	— —	45 49	Three weekly.
10	49	F	Schizophrenia, paranoid	13 years	75 70	20 —	— —	78 83	One weekly.
11	43	F	Manic-depressive psychosis, depressed.	8 months	73	78	78	1	
12	48	M	Manic-depressive psychosis, depressed.	2 years (5 months)*	66 89 53 51	0 0 35 —	19 33 — —	1 10 14 16	Ten, given three times weekly; then 4, twice weekly; then 2, once weekly.
13	49	F	Psychoneurosis, reactive depression.	1 year	95	55	—	1	
14	52	M	Manic-depressive psychosis, depressed	3 years (3 months)*	72 64	36 —	— —	11 14	Nine, given three times weekly; then 5, once weekly.
15	60	F	Manic-depressive psychosis, depressed.	6 years (6 weeks)*	93 33 77	38 41 43	— — —	4 7 8	Three times weekly.
16	52	F	Manic-depressive psychosis, depressed	3 weeks	56 81	15 13	0 33	2 8	Two, given once daily; then 7, given three times weekly.
17	47	M	Manic-depressive psychosis, manic	3 months	75 63 82 63	49 15 — —	— — — —	1 7 11 13	Ten, given three times weekly; then a rest of a week; then three times weekly.
18	50	M	Psychoneurosis, reactive depression	3 months	77	48	85	1	
19	50	F	Psychoneurosis, reactive depression	2 years	55 55	30 0	— —	6 8	Three times weekly.
20	60	F	Involutional psychosis, melancholia	18 months	70	0	4	9	Three times weekly.

* Duration of present attack.

blood. After electro-shock was given, decreases in eosinophilic cell count were found at the end of four hours in all patients but 2 (Cases 5 and 6); in the second of these, a fall of 60 per cent occurred at the end of eight hours after the treatment. In 3 instances (Cases 6, 11, and 15) the changes found at the end of eight hours were larger than those at the end of four hours after treatment, but the differences were not significant in two of these studies (Cases 11 and 15). Of the 13 measurements made at the end of twenty-four hours after treatment, the changes were more marked at this

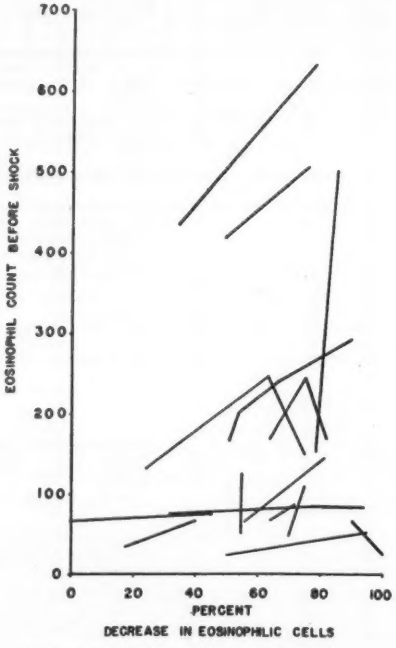

FIG. 1. Relation between initial eosinophilic cell count and magnitude of decrease after electrically induced convulsions.

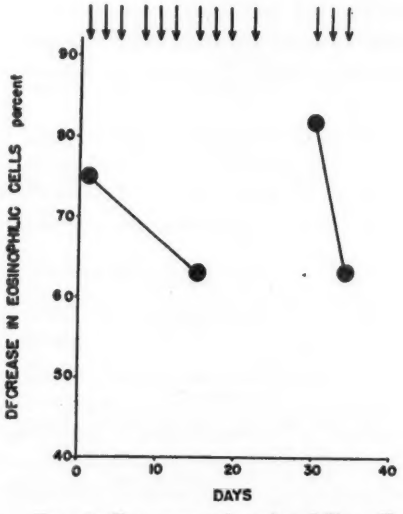

FIG. 2. Recovery of eosinophilic cell response to electroconvulsive therapy after a period of rest. Arrows indicate shocks.

time than at eight hours in 7 (Cases 3, 8, 12, 16, 18, 20) and were the same in 2 (Cases 8 and 11); indeed in 2 experiments the decrease in blood eosinophilic cells was slightly greater at twenty-four than at four hours after the treatment (Cases 6 and 11).

The amount of decrease in eosinophilic cell count after electroshock varied (Fig. 1). All patients studied on the occasion of the first treatment showed decreases in counts of at least 63 per cent irrespective of diagnosis and duration of illness (Cases 1, 2, 11, 12, 13, and 18). When treatments

were continued at frequent intervals, *i.e.*, every five days or more often, the amount of decrease in eosinophilic cell count after each shock lessened (Cases 1, 2, 3, 9, 14, and 17). In the case of patients given treatments once a week, insignificant lessening of the response of the eosinophilic cells occurred in two instances (Cases 7 and 10) and a significant lessening was found in one (Case 4).

Recovery of the eosinophilic cell response occurred after rest periods of ten days or more (Fig. 2). This was clearly indicated in two patients (Case 4 and 17) and suggested by the data in one other (Case 1). The finding of a greater response after the eighth than after the second treatment in one patient (Case 16) is probably due to the fact that the second shock followed the first by only one day, whereas all the other shocks given this patient were separated by intervals of two or three days. The small response found after the seventh treatment in Case 15, followed by a large change after the eighth is consequent to the fact that the administration of the treatment caused only a brief period of unconsciousness and no convulsion on the occasion of the seventh shock.

TABLE 2. DECREASE IN BLOOD EOSINOPHILIC CELLS 4 HOURS AFTER TREATMENT

Case 21 (age 65; involutional psychosis, melancholia)

Date	Decrease per cent	Type of treatment
5–28–48	93	Adrenocorticotropic hormone, 10 mg.
6–16–48	63	First shock
6–28–48	68	Sixth shock
7–2–48	54	Eighth shock

One patient (Case 21, Table 2) was given 0.6 Gm. of adrenocorticotropic hormone[1] in a period of eighteen days. On the first day of this period the injection of the hormone resulted in a decrease of eosinophilic cell count of 93 per cent; at the end of the eighteen days of treatment the patient was not improved clinically and had lost ten pounds in weight. She was then given eight electroconvulsive treatments over a period of sixteen days; during the course of three of these treatments, studies of the eosinophilic cells showed a lesser decrease than after the administration of hormone (Table 2). She gained six pounds and was discharged clinically well after these treatments.

[1] This was Adrenocorticotropin, Lot G-59703, kindly supplied by Dr. John R. Mote of the Armour Laboratories.

DISCUSSION

The results of the present study afford additional data supporting the concept that the adrenal cortex is stimulated during the course of electroconvulsive therapy. The decrease in eosinophilic cell count interpreted as evidence of adrenal cortical activity occurred after electrically induced convulsions in patients irrespective of diagnosis or of duration of illness; there was no correlation between the magnitude or persistence of the eosinophil response and the degree or persistence of clinical improvement resulting from the shock treatments given.

The response of the eosinophilic cells decreased with frequently repeated shocks in a manner reminiscent of the findings of Hills and associates (9) after daily injections of adrenocorticotropic hormone. However, the response returned in the present study after rest periods of ten or more days.

Available evidence indicates that the eosinophilic cell response is consequent to the action of 11-oxysteroids (8, 9, 10). It is evident from the present data that the steroid hormone responsible for the decrease in blood eosinophilic cells after electrically induced convulsions does not give rise to the clinical remission of mental disease secured by shock therapy. Accordingly, it must be concluded that increased production of the 11-oxysteroid hormones does not give rise by itself to the beneficial effects of shock therapy. A previous study (4) ruled out the 3-ketosteroids as effective in this direction. Clinical observations (7) suggest that the hormones which may be responsible for the beneficial effects of shock therapy have anabolic effects. Further studies of the last-named steroid hormones in regard to mental disease are clearly indicated.

SUMMARY AND CONCLUSIONS

Patients given electroconvulsive therapy for mental disease exhibit decreases in blood eosinophilic cell counts irrespective of diagnosis, duration of disease and clinical response to the shock treatment. The change in eosinophilic cell count tends to become less marked when treatments are given frequently and may return to its former level after a rest period of more than ten days.

In one instance the effect of adrenocorticotropic hormone (Armour) was compared with that of shock therapy, both given over a period of several weeks. The hormone caused a marked eosinophilic cell response but no clinical improvement whereas the convulsions caused a lesser eosinophilic cell response but resulted in clinical remission.

It is concluded that increased production of 11-oxysteroids, considered to be responsible for the eosinophilic cell response, is not the cause of clinical remission in patients given electroconvulsive therapy.

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THIOCYANATE GOITER WITH MYXEDEMA

REPORT OF TWO CASES*

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WITH the use of the thiocyanates as therapeutic agents in the treatment of hypertension, thiocyanate goiter has been well established as an entity. The existence of clinical myxedema in association with thiocyanate goiter has been reported. Wald and associates (1) were among the first to report on the formation of a goiter and a decreased metabolic rate in patients receiving thiocyanates for hypertension. Foulger and Rose (2) reported one case in which a goiter and clinical signs of myxedema developed during the course of treatment with thiocyanate. In a case reported by Kobacher (3) myxedema developed, with classical physical findings and a basal metabolic rate of minus 30 per cent. Rawson and coworkers (4) reported two cases, both with goiters and both having levels of protein-bound blood iodine characteristic of myxedema. A biopsy specimen from one patient was reported as revealing an extremely hyperplastic thyroid with marked papillary overgrowth. Potter (5), reporting on the pathology of two goiters (undoubtedly of thiocyanate origin) surgically removed, found brilliantly-staining colloid and no papillary infoldings into the acini. Preoperatively, one goiter was suspected of being carcinomatous and the other of being an acute swelling due to hemorrhage into an adenoma. Motley's (6) patient, to whom thiocyanate had been given for less than a year, had a goiter and a "general appearance quite suggestive of myxedema." Fahlund (7) reported a painful enlargement of the thyroid gland as a manifestation of thiocyanate sensitivity.

A study of the production of thyroid hyperplasia and some of the other abnormal thyroid changes which occur in rats made goitrous by thiocyanates has been accomplished in several laboratories. Astwood (8) included thiocyanate with a large group of antithyroid drugs and reported its hyperplastic action on the thyroid. Rawson *et al.* (9) produced goiters in rats on an iodine-deficient diet followed by addition of potassium thiocyanate to the drinking water. Four hours before killing the rats, the

Received for publication August 2, 1948.

* This work was done in part under an American Cancer Society Fellowship recommended by the Committee on Growth of the National Research Council.

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source of KSCN was removed and they were given radioactive iodine. The goiters produced by KSCN took up an average of 80 per cent, and the control glands 50 per cent of this material. The authors concluded that KSCN inhibited formation of the thyroid hormone, which resulted in hyperplasia of the thyroid and an increased avidity for iodine. On the other hand VanderLaan and Bissell (10) reported that the action of thiocyanate is one which prevents the uptake of iodine by the thyroid, but that this action can be overcome by giving an excess of iodine. Wolff *et al.* (11), reporting on this mechanism, found that as long as the blood level of KSCN remained high, the thyroid was prevented from taking up iodine. The high level of KSCN was shown by these investigators to exert this blocking effect both *in vitro* and *in vivo*. They concluded that there was rapid elimination of the KSCN from the blood, probably complete in twenty-four hours, in the rat. They would explain Rawson's results on this basis, by saying that the KSCN blood level fell during the four hours the rats were not receiving the drug and iodine was able to enter the hyperplastic gland.

CLINICAL MATERIAL

We are reporting two more patients who developed myxedema and goiters as the result of taking thiocyanate.

Case 1: J. H., MGH No. 113448, a 51-year-old white business man entered the Eye Clinic of the Massachusetts Eye and Ear Infirmary on September 9, 1947, complaining of puffy eyelids. A mild conjunctivitis was noted and treated. On a return visit, three weeks later, because he complained of persistent puffiness of the eyelids and enlargement of his neck, he was referred to the Medical Service of the Massachusetts General Hospital for study.

On October 15, 1947, he was seen in the Thyroid Clinic where further history revealed cold intolerance, decreased perspiration, lassitude, and somnolence, and a gain in weight of 8 pounds during the preceding four to six months. He stated that he had been taking a liquid "nerve medicine" for the past two and one-half years because of high blood pressure.

Physical examination, at this time, revealed a well developed, somewhat obese, jolly male in no evident distress. The skin was warm and dry. There was moderate periorbital edema without conjunctivitis, and examination of the fundi revealed minimal arteriovenous nicking. The tongue was wide and thick, the speech slow, and the voice of deep pitch. The thyroid gland was enlarged to 2 or 3 times normal size and was soft without nodules, bruit or thrill. The heart was of borderline size, the pulse rate was 60 and the blood pressure was 168/104. A smooth nontender liver edge was felt 2 finger breaths below the right costal margin. Laboratory data showed a basal metabolic rate of minus 38 per cent, blood cholesterol 298 mg. per cent, protein-bound iodine 1.7 gamma per cent (normal 3.5 to 7), and a urinary excretion of radioactive iodine of 50 per cent (probably normal). The patient was instructed to stop taking the "nerve medicine" at the time the radioiodine was started.

He was admitted to the medical wards on October 24, 1947, with a diagnosis of myxedema with goiter. At this time the physical examination was essentially the same except that the face was ruddy in color, the skin somewhat moist, the pulse rate 80, and the

blood pressure 170/100. The basal metabolic rate was minus 20 per cent four days after arrival on the ward. Routine urine and blood studies gave normal results. The blood cholesterol was 198 mg. per cent, NPN 26 mg. per cent, and total protein 6.6 Gm. per cent. An electrocardiogram revealed changes consistent with hypertensive and coronary artery heart disease.

Investigation of the "nerve medicine" revealed it to be a proprietary drug containing sodium thiocyanate, 4 Gm. per 100 cubic centimeters. Calculations showed that the patient had taken between 0.2 and 0.6 Gm. daily for two and one-half years. A blood level equivalent to 5.5 mg. per cent of KSCN was found two weeks after the drug had been stopped. (Our laboratory reports all thiocyanate in blood as KSCN equivalents.)

During seven days on the ward a definite decrease in the amount of periorbital edema was noted as well as a marked increase in the patient's activity. A second protein-bound blood iodine taken on October 29, 1947, was 3.4 gamma per cent and a second radioactive iodine excretion was 30.4 per cent (Table 1).

The patient was seen in the Thyroid Clinic on November 12, 1947, at which time he had no complaints other than slight cold intolerance. Only very slight periorbital edema remained, the speech seemed normal and the thyroid gland had decreased in size and was of firmer consistency. The basal metabolic rate was minus 13 per cent.

Case 2: Mrs. H. A. MGH No. 420648, a 64-year-old white widow was referred on September 19, 1947, to the Thyroid Clinic from the Out-patient Department of the Massachusetts General Hospital because of a nodular goiter.

She was first seen in the Medical Clinic in September 1943 with a nine-year history of hypertension. At this time, her blood pressure was 220/115. The blood cholesterol was 275 mg. per cent and there was described a single 2-centimeter nodule in the right lobe of the thyroid. Phenobarbital was prescribed, and she was followed until February of the following year.

She was next seen in the Medical Clinic in July 1947, where her mild cardiac decompensation responded to digitalis. Her blood pressure was 200/90. On August 12, without our knowledge, her private physician prescribed KSCN capsules, 0.2 Gm. daily. On August 18, the blood pressure was 175/75, the blood NPN was 18 mg. per cent, the blood cholesterol 250 mg. per cent, and the blood counts and urinalysis were essentially normal.

On September 19, she was referred to the Thyroid Clinic for the first time. Her complaints were recent onset of deafness and intractable constipation. The basal metabolic rate was minus 11 per cent and the pulse rate 60. There were no other signs of hypothyroidism and the gland was essentially normal except for a 2-centimeter nodule in the lower right lobe.

On November 5, 1947, she again returned to the Thyroid Clinic complaining of deafness and intractable constipation. In addition to these, she had noted marked cold intolerance, absence of perspiration, and dryness of her skin. She presented, on physical examination, rather marked facial and periorbital edema, dry skin, and cold extremities. She was distinctly pale and abnormally hoarse. The palpable thyroid tissue was little changed from her first visit. A blood protein-bound iodine was 0.6 gamma per cent (Table 1). A diagnosis of early myxedema was made. At the time of this visit it was learned that she had been taking thiocyanate capsules. However, the patient stated that she had taken the capsules for only five weeks after they were first given to her in August, and that she had had none since her first visit to the Thyroid Clinic on September 19.

On November 20, a tracer of radioactive iodine was administered and 33 per cent was excreted in the urine. On November 22, a serum thiocyanate level was 4.9 mg. per cent

and the blood protein-bound iodine had risen to 3.3 gamma per cent. On December 12, the blood iodine level was 4.3 gamma per cent, the urinary excretion of a second radioactive iodine tracer dose was 48 per cent, and a blood KSCN level was 1.8 mg. per cent.

At the present time, five months after she was first seen in the Thyroid Clinic, she has none of the former symptoms or signs of hypothyroidism and is subjectively well.

TABLE 1

Patient No.	Length of time thiocyanate administered	Date thiocyanate omitted	Date of laboratory data	Basal metabolic rate %	Protein-bound blood iodine, gamma %	Urinary excretion of radioactive iodine, (per cent of administered dose)
1	30 months	10/15/47	10/15/47	−38	1.7	50
			10/28/47	−20		
			10/29/47		3.4	30.4
			11/12/47	−13		
2	5 weeks	9/19/47	9/19/47	−11		
			11/ 5/47		0.6	
			11/20/47			33
			11/22/47		3.3	
			12/12/47		4.3	48

DISCUSSION

Two patients, during thiocyanate treatment for hypertension, developed clinical myxedema with levels of basal metabolism and protein-bound blood iodine characteristic of this disease. After thiocyanate therapy was discontinued, the myxedema disappeared and the basal metabolic rate and the blood protein-bound iodine returned to normal.

The uptake of radioactive iodine in the first case was at first normal, then high. Apparently the level of thiocyanate in the blood was high enough to block partially the radioactive iodine uptake at the time of the first dose, but as the level fell, the depleted hyperplastic gland was able to take up iodine in larger quantities. It can be anticipated that iodine uptake in

Case 1 will return to normal as it did in Case 2, in which instance the gland required less iodine as it returned to the normal production of hormone. This production was reflected in the rising protein-bound iodine of the blood.

The first patient did not develop myxedema until he had taken thiocyanate for two years. The second patient developed myxedema after one month of thiocyanate therapy. The reason for this difference is not evident.

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ADRENAL CORTICAL CARCINOMA IN A MALE WITH EXCESS GONADOTROPIN IN THE URINE

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TUMORS of the adrenal cortex with symptoms of hypercorticoidism are infrequent (1–3). Most of the cases reported presented masculinization (in females) or the adrenogenital syndrome (in males or females); a few showed evidence of feminization (in males)(4–12). Adrenal cortical tumors associated with excess gonadotropin seem to be exceedingly rare. A search through the literature revealed only one case (McFadzean) (13):

> The 29-year-old patient was admitted because of unexplained fever. He gave a history of symptomless breast enlargement of eighteen months' duration, of weight gain of one year's duration, and of decreased sexual activity and libido of six months' duration. A large tumor mass was palpable in the upper left quadrant. The breasts were well developed, the genitalia were normal, and there was a slight feminine distribution of his hair. X-ray examination showed a soft tissue mass with displacement of the left kidney. The lungs were clear. Urinary estrogens or gonadotropins were not assayed, but a Friedman test was positive. Twenty days after successful removal of the tumor, the Friedman test was found to be negative. Sexual interest and activity returned, and by the forty-third postoperative day the beard was thicker and periareolar hair had grown. The tumor was mostly encapsulated, multilobulated and weighed 1420 Gm. It showed fibrous cores, multiple hemorrhages and light gray areas, and one lobe resembled the "classical hypernephroma." Microscopic examination revealed an adenocarcinoma, the structure resembling that of adrenal cortex with various types of nuclei and some vacuolization.

As only one case was found in the literature, it seemed of interest to report another case in which both Friedman tests and gonadotropin assays were made.

CASE REPORT

Present illness: The patient was a white male, 39 years old at the time of his first hospital admission July 31, 1947. The presenting complaints were cough with hemoptysis, hematuria occurring at the end of micturition, bloody ejaculation and continuous progressive pain in the left arm and both flanks. These complaints had developed over the preceding ten or eleven weeks. Diagnosis of metastatic malignancy was made, although the primary site was not discovered. The patient received deep x-ray therapy (8 series, 200 r) before his discharge on August 22. At the time of the second hospital admission in September 1947, he stated that all symptoms had persisted and progressed in severity except the hematuria. In addition, the breasts had become sore. The flanks, which ached continuously were sore to the touch, and pain in the chest accompanied the productive cough. On being questioned, the patient stated that he had noted continuous right frontal headache and pain in the right eye, but no impairment of vision. Eight days prior to the

Received for publication September 1, 1948.

second admission, nausea and vomiting had occurred without pain or hematemesis. There had been recent constipation, but no hemorrhoids or melena. Marked weakness was reported.

Physical examination: The patient was a well developed, fairly well nourished, white man who appeared acutely ill. He had a paroxysmal cough productive of bloody sputum. Extreme tenderness and pain accompanied movement of all extremities, particularly the left shoulder and arm. Positive findings in the mouth and throat were dental caries and enlarged tonsils. On examination of the chest there was tenderness of the nipples but no enlargement of the breasts. Breath sounds were decreased bilaterally but there were no rales or alteration of fremitus. The heart was normal in size, the sounds were clear, and the rate was 100 with irregular rhythm. An abdominal mass the size of an orange was palpable in the right upper quadrant laterally, with tenderness present over the mass and tenderness in the left lower quadrant near the ileum. No other organs or masses were palpable. The genitalia were normal in size and appearance. No blood or discharge could be expressed from the urethra, but the prostate was slightly enlarged and soft. A large soft fixed lymph node was palpable in the left axilla. Except for absence of the left triceps, biceps and wrist jerks, the neurologic findings were normal.

X-ray and laboratory data: First admission (Mt. Sinai Hospital):[1] An x-ray picture of the chest was interpreted as showing a metastatic malignant lesion. An intravenous urogram demonstrated ptosis and slight enlargement of the left kidney. No additional information was obtained from cystoscopic examination, urine examination for acid-fast organisms, x-ray examination of the left shoulder girdle, left arm and gall bladder, gastro-intestinal series and barium enema. Bronchoscopy in August 1947 was reported as showing "a compression of the right lateral and posterior walls of the mid-trachea by an external mass which cut the lumen by one-third. The overlying mucous membrane was normal; otherwise the bronchoscopic findings were normal." Bronchial secretion was devoid of acid-fast organisms and malignant cells. The Friedman test was reported positive August 18, and the positive finding confirmed on a second test. Study of urinary hormone output on September 2 showed the patient was excreting 50,000 mouse units of Prolan A per 100 ml. of urine.

Second admission (Philadelphia General Hospital): X-ray examination of the chest showed metastatic malignancy throughout. Additional x-ray studies revealed early metastatic lesions of the lower left humerus and an enlarged right kidney, but no evidence of metastases to the skull, vertebrae or pelvic bones. An intravenous pyelogram demonstrated impaired function of the left kidney and a large irregularity suggesting primary malignancy. The right kidney functioned normally. Blood studies revealed 2.78 million erythrocytes and 10,850 leukocytes. There were 77 per cent polymorphonuclear cells, 21 per cent lymphocytes, 1 per cent monocytes and 1 per cent eosinophiles. Sugar was 81 mg. per cent, urea nitrogen 14 mg. per cent, and total protein 6.0 Gm. per 100 ml. with an A/G ratio of 3.4:2.6. The CO_2 combining power was 17.6 mEq. and Cl (NaCl) 104.5 mEq. per liter. A Kline test was negative. Urinalysis showed a specific gravity ranging from 1.009 to 1.017. There was an occasional 1 plus albuminuria, and the sediment showed 10 to 15 erythrocytes per high power field and many leukocytes.

Course: In spite of treatment by bed rest, opiates for relief of severe pain, and an indwelling catheter, the patient followed a rapidly declining course with gradual onset of severe dyspnea, and died October 16, 1947.

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[1] I am indebted to Dr. D. Meranze for letting me use these data.

Postmortem examination: The body was that of an extremely cachectic white male. The distal end of the left arm was diffusely swollen. The breasts were grossly normal. The serous membranes were all smooth and glistening and no adhesions or fluid were found. The vessels were normal throughout. There was no arteriosclerosis. The heart weighed 280 Gm. It was flabby and showed slight dilatation of the left ventricle and marked dilatation of the right ventricle. The left lung weighed 1300 Gm., the right 1800 Gm. External surfaces were smooth, blackened and nodular. Throughout the parenchyma of each lobe hard, purplish white nodules, measuring approximately 2 to 3 cm. in diameter, were found. The intervening lung tissue was congested. Bronchi and vessels were clear.

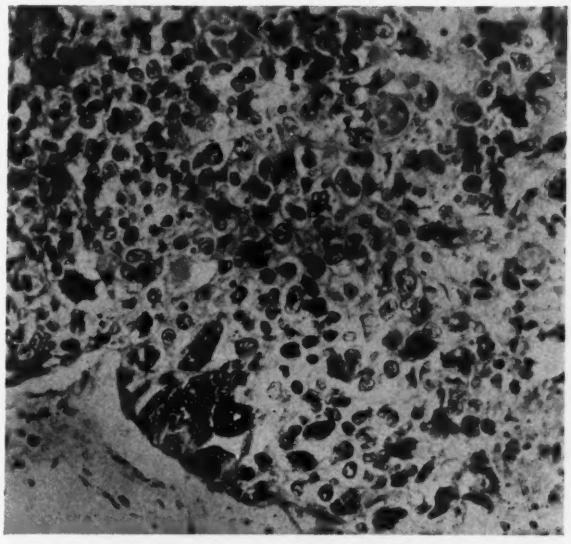

FIG. 1. Portion of tumor forming solid sheets of polygonal cells including giant cells with large hyperchromatic nuclei. Hematoxylin-eosin, ×250.

The spleen weighed 80 Gm. The capsule was smooth. The consistency was soft. The color was purplish. There was no evidence of tumor. The mesentery and mediastinal lymph nodes were enlarged and replaced by tumor tissue. The external nodes were normal. The left kidney weighed 330 Gm., the right 180 Gm. The entire lower pole of the left kidney was replaced by a tumor mass, measuring 8 cm. in diameter. It was round with an irregular surface, and on cut surface was white in color with streaks of purplish red. In the midportion of the left upper lobe, a firm, round nodule measuring approximately 2 cm. in diameter was found. It was purplish-red in color but did not show as much firm, white tissue as the one in the lower lobe. The remaining parenchyma was pale and somewhat cloudy. The right kidney contained several small purplish nodules measuring from 1 to 2 cm. in diameter. Renal pelves were normal except for distortion by tumor masses. The ureters were normal. The urinary bladder was not changed. Both testes were normal in size and consistency. The prostate was normal. The esophagus, stomach and bowel were not changed. The mesentery of the small bowel contained small metastatic nodules approximately 1 cm. in diameter, which were of the same consistency as the tumor tissue elsewhere. The liver weighed 2330 Gm. The interior and lateral portions of the right lobe

contained a tumor mass approximately 12 cm. in diameter causing extension of this lobe down to the iliac crest. There was a small metastatic nodule near the diaphragmatic portion and several very small nodules throughout the inferior portion of the left lobe. The latter nodules were purplish in color, while the large mass in the right lobe was white. The remaining liver substance was pale brown and somewhat greasy. The portal venous system was normal. Gall bladder and bile ducts were normal. The pancreas contained several small tumor nodules within the body, each approximately 1 cm. in diameter. The duct appeared to be normal. The left adrenal appeared to be normal. The right was changed into a round, firm, well encapsulated mass measuring 3 cm. in diameter. On cut section, it was homogeneously purplish in color and distinctly firm throughout. The thyroid appeared to be normal. The distal end of the left humerus was completely sur-

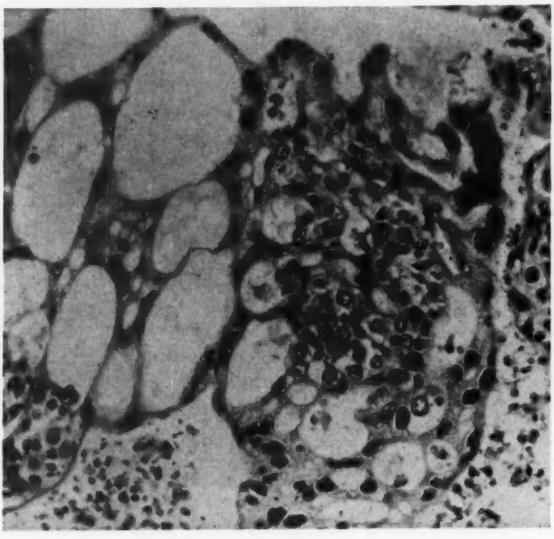

FIG. 2. Portion of tumor forming spaces lined with epithelial cells resembling chorion epithelium. Hematoxylin-eosin, ×250.

rounded by tumor tissue, similar to that described above. It was approximately 1 to 1½ cm. thick in all areas around the distal end of the bone and appeared to replace the periosteum. The underlying bone was rough and irregular. The tendon of the triceps brachii was completely replaced by this mass in its distal portion. The humerus was free below the condyles and below the mid-portion. On section, the tumor did not invade the bone at all, although the medullary substance was soft and of purple color. The remaining bones appeared to be normal. Brain and pituitary were not examined.

Microscopic examination: In some places, such as the lungs (Fig. 1), the tumor formed solid sheets of large polygonal cells with large somewhat vesicular nuclei not unlike the cells of the adrenal cortex. There were occasional giant cells with large hyperchromatic nuclei. There were many mitotic figures. In other places, such as in the liver (Fig. 2), the tumor formed bizarrely shaped spaces often lined with large endothelial-like epithelial

cells resembling chorion epithelium. The latter formed multinucleated giant cells in places. The small spaces surrounded by these cells contained protoplasmic debris and plasma, while the large ones contained erythrocytes and leukocytes as well. These portions of the tumors, too, contained abundant mitotic figures. All tumors showed more or less extensive necrosis. The one in the right adrenal gland was almost completely necrotic. There was little fat in the tumor cells except in the areas where they underwent necrosis.

The testes were somewhat atrophic. Spermatogenesis was almost completely suppressed. The spleen showed chronic splenitis with a good many plasma cells and eosinophiles. The lungs, liver and kidneys were markedly congested, and there was extensive central necrosis of the liver lobules.

The *final diagnosis* was carcinoma of the cortex of the right adrenal with metastases to lymph nodes, lungs, liver, kidneys, pancreas and left arm. Cause of death was repiratory and circulatory failure.

COMMENT

The case of adrenal cortical carcinoma reported here resembled that of McFadzean's (13) in that the patient was a male, and excess gonadotropin was excreted in the urine; it differed in that it showed no convincing evidence of feminization. In the case of a male reported by Simpson and Joll (11) endocrine assays revealed excess estrogen excretion in the urine, but the Aschheim-Zondek test was negative, and no gonadotropin was demonstrable. These observations seem to show that adrenal cortical carcinomas may be associated with either excess estrogen excretion or excess gonadotropin excretion or both.

The cellular sources of gonadotropins are generally believed to be the chorion epithelium of the placenta and the anterior lobe cells of the pituitary gland. In the case reported here, as in McFadzean's case, we have no evidence that the gonadotropins were produced by either placental tissue or the pituitary gland. In our case, the histologic structure of the tumor resembled that of adrenal cortex in most places, though here and there the cells showed differentiation towards elements resembling chorion epithelium (Fig. 2). In McFadzean's case, the Friedman test became negative promptly after successful removal of the tumor; whereas in cases with excess hypophyseal gonadotropin excretion secondary, for instance, to seminoma testis, successful treatment of the tumor is said not to cause a prompt fall in gonadotropin and the hormone continues to be excreted in the urine in excessive amounts for some time (13). Moreover, McCullagh and Cuyler(14) reported a case of Cushing's syndrome due to a pituitary adenoma in a woman with a positive reaction to the Friedman test. Her symptoms and the gonadotropin excretion all disappeared following denervation of both adrenals and right hemiadrenalectomy, without therapy to the pituitary gland. These observations seem to indicate that the adrenals may be instrumental in the elaboration of gonadotropic hormones.

SUMMARY

A case of adrenal cortical carcinoma in a man with excess gonadotropin excretion is reported. The patient excreted 50,000 mouse units of gonadotropin per 100 ml. of urine and the Friedman test was positive.

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GYNECOMASTIA IN PARAPLEGIC MALES

REPORT OF SEVEN CASES

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THE authors wish to report 7 cases of gynecomastia occurring in paraplegic males. These cases are believed to be significant for the following reasons: 1) Out of 32 paraplegic patients on our ward at one time, these 7, or 22 per cent of the paraplegic patients at that time under our observation, showed gynecomastia. 2) All of these patients were young males of military age, and all were paraplegic due to traumatic injuries of the spinal cord. 3) The physiologic implications of this syndrome may be of practical value as well as academic significance.

Our attention was first called to this unusual syndrome by the patients on the paraplegic ward who had singled out one of their number by referring to him as "Mae West." It was then apparent to us that this patient had developed a bilateral enlargement of both breasts, and, in a survey of the 32 patients on the ward at that time, 7 of the patients proved to have either bilateral or unilateral gynecomastia. Several stated that the enlarged breast was tender, and a few of the patients who did not show evidence of gynecomastia at that time believed that they had had enlarged breasts at some time during their illness.

Gynecomastia has been reported in many diverse clinical entities. In 1944 Webster (1) reported that in the years 1939 through 1941, from 6.9 to 8.69 otherwise normal males out of every 100,000 men entering the navy showed gynecomastia. Our incidence of 22 per cent in this series of paraplegics, contrasted to 8 per 100,000 in normal males of the same age group, would appear to be strikingly significant. The finding of gynecomastia in liver disease, particularly cirrhosis, is a well documented observation (2). It has also been reported as a consequence of desoxycorticosterone acetate (DOCA) therapy in both mice (3) and humans (4), in Addison's disease (5), in vitamin deficiency (6), in a case of choriocarcinoma of the testis (7), in a man with bilaterally undescended testes (8), in a case of extragenital chorionepithelioma (9), and in other diverse disease entities. At first glance, an etiologic common denominator underlying these various disease states which have been reported as being instrumental in producing gynecomastia, is not apparent. However, there are several endocrinologic factors which most of the reported cases might conceivably have in common.

Received for publication August 11, 1948.

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Edmonson, Glass, and Soll (2) have demonstrated the fact that the degeneration of the liver parenchyma causes an excess of estrogen in the systemic circulation, and thus suggest an endocrinologic basis for the breast hypertrophy in cases of liver disease. Klinefelter, Reifenstein, and Albright (10) reported a syndrome characterized by gynecomastia, aspermatogenesis without a-leydigism, and increased urinary excretion of F.S.H. (follicle stimulating hormone). In these cases the testes were small, measuring about 1.5×1.0×0.5 cm., the urinary 17-ketosteroid levels varied from relatively normal to definitely subnormal, and the testicular biopsy revealed primarily a hyalinization of the tubules. This syndrome has also been reported by Bettinger and Robinson (11), and more fully by Heller and Nelson (12). Klatser, Salter and Humm (13) reviewed very carefully 48 cases of gynecomastia occurring among prisoners of war who had been suffering from malnutrition. Their clinical studies revealed abnormalities of both the liver and the genitalia in these patients. The same authors (14) reported that these patients suffering from malnutrition, and demonstrating gynecomastia, were found to have significantly lowered 17-ketosteroid levels in the urine. However, urinary estrogen values were in the low normal range, the cortin levels were normal, and there was no apparent increase in the urinary titer of F.S.H. Therefore, at this time, there is no clear cut, general interpretation of all of the endocrinologic factors in the pathogenesis of gynecomastia. These cases of gynecomastia in paraplegics may serve to add another link in the chain of information leading to an understanding of this entity.

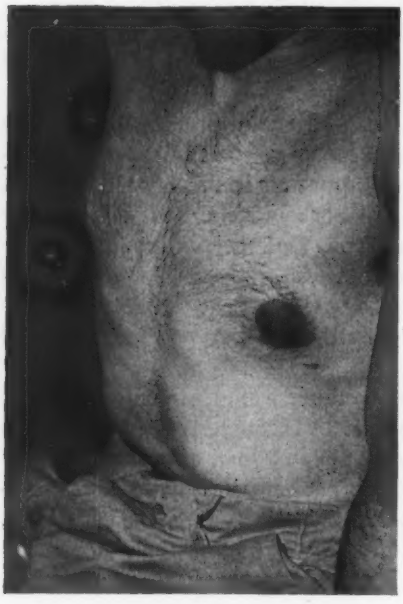

FIG. 1.

CASE REPORTS

Case I. W.E.M., a 20-year-old private in the Marine Corps, was injured in April 1945, with a resultant paraplegia below the level of the twelfth thoracic dermatome. He had lost 75 pounds during the subsequent four months but by May 1946, had returned to his normal weight. Bilateral gynecomastia was first noted in May 1946 (Fig. 1).

Case II. J.S., a 39-year-old chief carpenter's mate in the Navy, was paraplegic below

the level of the first lumbar segment as a result of a fracture dislocation of the vertebral column incurred in a fall. Bilateral gynecomastia appeared approximately eighteen months following the injury. Incidentally, the patient had had his left testis surgically removed because of a tumor therein. This operation took place overseas during the war, and no pathologic report was obtainable.

Case III. W.W., a 22-year-old corporal in the Marine Corps, was rendered paraplegic by shrapnel wounds of the spinal cord. A unilateral (left) gynecomastia was observed fourteen months later. The patient could not state how long this breast had been enlarged.

Case IV. A. W., a 26-year-old Marine private, was paraplegic below the ninth thoracic segment as a result of a shrapnel wound of the spinal cord. Bilateral gynecomastia appeared approximately ten months following the injury and had been present for three months at the time of observation.

Case V. T.R.K., a 19-year-old private in the Marine Corps, was paraplegic below the sixth thoracic segment as a result of a bullet wound of the spinal cord. Unilateral (left) gynecomastia was first noted fifteen months after the injury.

Case VI. W.W., a 22-year-old seaman second class in the Navy, was rendered paraplegic from wounds received from machine gun bullets. A unilateral (left) gynecomastia was noted approximately sixteen months following this injury. This patient had a recurrent left epididymitis as a result of infection from an indwelling urethral catheter.

Case VII. E.S., Jr., a sergeant in the Marine Corps, had complete motor and sensory loss below the sixth thoracic dermatome, following a motor vehicle accident in which he incurred a compression fracture of several thoracic vertebrae. A bilateral gynecomastia was noted twenty months after this injury.

We were able to obtain single F.S.H. studies on the urine of patients II, IV, and VI. In cases II and VI there was a positive reaction for 96 mouse units in a twenty-four hour specimen, this being a pathologically significant elevation of F.S.H. Measurements of the testes of all 7 patients were in the low normal range. Only 1 of the 7 was able to have ejaculation of semen, and this was free of motile sperm. In only 1 of these cases was malnutrition considered to have been a prominent feature, and 2 of the cases showed testicular pathologic processes, as noted in cases II and VI above.

Possible Pathogenesis of Gynecomastia in Paraplegics

At this time we can do no more than suggest certain hypotheses for the pathogenesis of the breast hypertrophy occurring in these paraplegics. Although the testicular measurements were within low normal limits, it is possible that these cases would fall into the same category as those described by Klinefelter, Reifenstein, and Albright. In 2 of the 3 cases in which urinary F.S.H. titers were obtained, there was a significant elevation of this gonadotropin. In only 1 of the 7 patients was there the power of ejaculation. None of these patients was willing to submit to biopsy of the testis. (All of these patients were engaging in autistic thinking as regards the return of sexual capacity and were unwilling to allow any procedure which might conceivably damage the sexual organs.) Thus it is seen that

at least 2 of these patients showed gynecomastia, aspermatogenesis, and increased F.S.H. excretion. It is not unlikely that further studies on similar patients may reveal these patients to be examples of the Klinefelter-Reifenstein-Albright syndrome secondary to traumatic lesions of the spinal cord.

Salter, Klatskin, and Humm (14) suggested that an involvement of the pituitary-gonadic axis might be the cause of the gynecomastia seen in prisoners of war suffering from malnutrition. It is possible that such an involvement may have caused the gynecomastia in our paraplegic patients. Selye (15) has demonstrated the degenerative changes that occur in the anterior lobe of the pituitary gland in the diseases which act as stimuli for the alarm or adaptation reaction. Spinal cord transection is one of the many stimuli which may produce the alarm reaction (16). Certain it is that these war-wounded paraplegics are subjects in whom the adaptation syndrome may well be expected to follow the severe trauma incurred. The secondary endocrinologic changes which may follow hypopituitarism are hypothyroidism, hypofunction of the adrenal cortex, and hypogonadism (17). It is not unlikely that the adaptation syndrome, with its consequent hypopituitarism, might be instrumental in bringing about hypogonadism, and thereby contribute to the pathogenesis of gynecomastia in paraplegia due to traumatic injuries of the spinal cord.

SUMMARY

1. Seven cases of gynecomastia occurring in young paraplegic males are presented. Four of these patients had bilateral breast hypertrophy and three had unilateral (left) gynecomastia.

2. Some of the theoretical considerations regarding the pathogenesis of gynecomastia in these cases have been presented.

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THE USE OF BISMUTH SALTS IN THE TREATMENT OF SPORADIC GOITERS

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THE therapy of simple goiter is practically limited nowadays to the use of iodine or desiccated thyroid and, finally, to surgical removal for cosmetic reasons. The purpose of this communication is to call attention to observations on another method which may conceivably prove to be of some value.

While treating some patients with bismuth salts in the routine treatment for syphilis, it was noted that a goiter, an incidental finding, was noticeably reduced in size during the treatment. Following this observation, a number of patients with goiter but without syphilis were deliberately treated with bismuth salts. In some instances there was a striking reduction in size, almost to normality. These results have been published in a preliminary report.[1]

No data having direct bearing on this subject could be found in the medical literature. The excellent studies on bismuth, of Sollman and coworkers, did not mention possible actions of bismuth on the thyroid; but since this gland has a large vascular supply, it may be that the amount present in the blood represents the amount in the gland. Bismuth is stored principally in the kidneys, in the amount of 3.33 mg. of bismuth per 100 Gm. of fresh tissue; the figure for the liver is 0.68 mg. and for the blood, 0.05 mg.

A long-standing enlargement of the thyroid which is symmetrical and firm and does not produce symptoms of hyperfunction, is very suggestive of simple goiter, particularly when this condition occurs also in other members of the family. Nodular enlargement may or may not be adenoma, because these irregular masses can also be in the nature of a simple goiter. Clinically, it is not very important to differentiate simple from nodular goiter, for both lack hyperfunction and their harm is merely local; yet both can assume hyperfunction in some instances, and both can disappear spontaneously.

MATERIAL AND METHODS

The treatment at first was confined to the simple and nodular goiters and later it was extended to include other thyroid conditions including hyperthyroidism. In these latter instances, the bismuth therapy invariably appeared to have no effect on the hyperthyroidism, but when this condition

Received for publication August 16, 1948.

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[1] Villaverde, M.: Bocios tratados con sales de bismuto, *Vida Nueva* (Havana), **58**: 233 (Dec.) 1946.

was controlled with thiouracil, the bismuth therapy was then followed by a reduction of the size of the gland to normality in two cases. It failed under similar conditions in one other case.

The patients in this series had moderately enlarged thyroids which, except in one instance, did not produce local distress. Most of the cases were considered to be simple goiter, although some had nodular enlargement and in the latter part of the series some patients with hyperfunction were also treated.

Therapy: The bismuth salts commonly used in the treatment of syphilis were employed, the subsalicylate and heptadiencarbonate being the most frequently used.[2] The patients were given 1 or 2 injections weekly, with a total of 20 injections in each series. There were intermissions of from two to four weeks between series. The injections were made into the gluteal region, and routine precautions against toxic reactions were taken, the gums and local area being inspected carefully and frequently.

Although no measurements of the thyroid were made, the enlargement was carefully estimated, and only when a striking decrease in the size of the gland was evident was a result set down as positive.

RESULTS

The results are listed in Table 1, which is for the most part self-explanatory.

In the following paragraphs are mentioned some of the salient features of the various cases:

There were 10 cases of diffuse simple goiter. The only males were *No. 1* and *No. 15*. The former had been treated with arsenic and bismuth for a syphilitic chancre but he had never shown positive findings in the blood. Two years after the treatment was discontinued his thyroid remained normal in size.

Case No. 3 showed hyperthyroidism with a very effective reaction to bismuth.

Case No. 4 showed very rapid improvement, the gland reaching normal size after 15 injections.

Case No. 5 was one of syphilis in which a goiter developed after antiluetic therapy; she also had hypertension.

Case No. 9. The patient failed to improve with bismuth; she ultimately developed tuberculosis after having had a severe bout of hyperthyroidism which improved with thiouracil.

[2] Bismuth subsalicylate (*Stabisol*, Squibb): Bi., 0.13 Gm. ×cc. (1 cc. once a week or ½ cc. twice a week).

Bismuth heptadiencarbonate (*Medobis*, Chinoin): Bi., 0.045 Gm. ×½ cc. (½ cc. twice a week).

TABLE 1

Case No.	Origin in endemic area	Family Background: Syphilis	Family Background: Endocrine	Family Background: Goiter	Personal history: Syphilis	Serologic tests	Endocrine symptoms	Goiter (diffuse or nodular)	Basal metabolic rate, %	Body constitution	Circulatory symptoms	Additional diagnoses	Number of series	Number of injections	Results	Remarks
1	+	−	+	+	−	−	−	D		III*	−	Syphilitic chancre	3	60	++++§	
2	−	−	−	−	−	−	−	D	+ 1	II	−		3	60	+++	
3	−	−	+	−	−	−	−	D	+34	II	+	Hyperthyroidism	2	40	+++	
4	−	−	+	+	−	−	−	D	−19	II	−		1	20	++++	Normality after 15 injections.
5	−	−	−	−	+	−	−	D	+ 9	II	+	High blood pressure	2	40	++	Goiter developed after treatment for syphilis.
6	?	−	−	−	−	−	−	D	+25	III	+		1	20	+	
7	?	−	−	−	−	−	−	D	± 0	II	±		2	39	+	
8	−	−	−	−	−	−	−	D	− 7	I	−		1	20	−	
9	−	−	−	−	−		−	D	+23	II	+	Hyperthyroidism	2	30	−	Intolerance to bismuth. Developed tuberculosis.
10	−	−	+	−	−	−	+	D	−33	II	−	Hyperostosis frontalis interna; anxiety neurosis	2	40	−	
11	+	−	+	−	−	−	−	N	−22	II	−	Backache	1	20	−	
12	−	−	+	+	−	−	−	N	− 5	II	−		2	40	+++	Iodine had failed previously.
13	−	−	+	−	−	−	+	N	+21	II	+	Hyperthyroidism	2	40	+++	Relapse after 10 weeks
14	+	−	−	−	−		+	N	−23	II	−	Hyperestrogenism	2	40	+	Discomfort disappeared on swallowing.
15	−	−	?	?	−	−	−	N	−13	II	−		2	40	++++	Normality before the end of the second series.
16	−	−	−	−	−	−	?	N	+17	II	+	High blood pressure	2	40	−	
17	−	−	−	−	−	−	−	D	+11	II	+	Graves' disease	1	20	−	
18	−	−	+	−	−	−	−	D	− 3	II	+	Basedow neurosis	1	20	−	

* III = pyknic type; II = asthenic type.
§ ++++ = gland restored to normal size.
+++ = almost normal size.
++ = distinct improvement.
+ = slight improvement
± = no improvement.

Case No. 10 was one in which there was no improvement with two series of treatment. The patient is now in the course of the third treatment. She shows an anxiety neurosis and a mild hyperostosis frontalis interna.

The next 6 cases (*Nos. 11–16*) are of nodular goiter.

Case No. 12 is noteworthy because of the success of bismuth therapy after the failure of iodine.

Case No. 13. The patient showed improvement after 40 injections. Treatment was then discontinued and during the following ten months her goiter showed renewed growth. She later developed hyperthyroidism.

Case No. 14 was one in which the goiter was associated with discomfort on swallowing. Following two series of treatments there was some decrease in size sufficient to cause the discomfort to disappear.

Cases No. 17 and *18* showed failure of bismuth therapy in Graves' disease.

DISCUSSION

There were good results in about 70 per cent of the cases treated and in 50 per cent of the cases the results were excellent; in some it was successful even when iodine had failed. Thus, of the 10 patients with diffuse goiter, 5 showed great improvement, 2 showed slight improvement, and treatment failed in 3 instances.

Among the 6 cases of nodular goiter, 3 showed great improvement, 1 improved only slightly, and 2 failed to improve.

In the 16 cases treated, 50 per cent showed great improvement, 19 per cent slight improvement, and 31 per cent failed to improve.

The duration of the treatment appeared to be important, for although 1 case was restored to normal before 15 injections were given, in the majority of the cases two series of treatments were necessary. The only 2 patients who received three series of injections showed great improvement. The following table indicates the dispersion of the cases with respect to the number of series of treatments:

Improvement according to the number of series of injections

	One series			*Two series*			*Three series*		
Improvement:	Great	Slight	None	Great	Slight	None	Great	Slight	None
No. of cases:	1	1	2	5	2	3	2	0	0

SUMMARY

Bismuth salts, the subsalicylate and the heptadiencarbonate such as are used in the therapy of syphilis, have been applied to the treatment of both diffuse and nodular goiter. In these cases the metallic ion seems to act upon the structure of the gland to reduce its size. It does not appear to alter its

function. The bismuth therapy was given in series of injections in accordance with the common practice in the treatment of syphilis, and was particularly successful when two or more series of injections were given. When hyperthyroidism was present, the therapy did not appear to alter the state of hyperfunction, but when this condition was controlled prior to the bismuth therapy, this treatment appeared then to reduce the gland to normal size. Fifty per cent of the cases of simple or nodular goiter showed great improvement; 20 per cent showed slight improvement and 30 per cent failed to improve.

The 1949 Meeting of the Association for the Study of Internal Secretions

FRIDAY AND SATURDAY, JUNE 3 AND 4

Headquarters: Chalfonte-Haddon Hall, Atlantic City, New Jersey.

Registration: Everyone attending the meetings is requested to register. A fee of $1.00 will be charged non-members of the Association. Membership cards should be presented when registering.

The Scientific Sessions: The Scientific sessions will be held in the Viking Room of the Haddon Hall Hotel and programs will begin promptly on schedule. Papers presented at all meetings are planned for ten minutes, unless otherwise noted, and owing to the heavy schedule must be kept within this limit. Manuscripts of all papers should be submitted to the presiding officer or Secretary-Treasurer at the end of the presentation.

Annual Dinner: The Annual Dinner of the Association will be held on Friday evening, June 3, at 7:30 o'clock in the Rutland Room of the Haddon Hall, preceded by cocktails at 6:30 o'clock in the West Room. Secure tickets at time of registration.

Council Meetings: There will be a meeting of the Council on Thursday afternoon, June 2, at 2:00 o'clock, and a luncheon meeting on Friday, June 3.

Business Meeting: The Annual Business Meeting of the Association and Election of Officers will be held at 4:30 p.m., June 4, in the Viking Room of the Haddon Hall.

Local Arrangements: Dr. Matthew Molitch, 705 Pacific Avenue, Atlantic City, New Jersey, is in charge of the local arrangements for the meetings.

Secretary-Treasurer: Henry H. Turner, 1200 North Walker Street, Oklahoma City 3, Oklahoma.

PROGRAM

FRIDAY, JUNE 3, 1949

9:15 a.m.—C. N. H. Long, presiding

1. Piperido-methyl-benzodioxane (933-F): Some Pharmacological and Experimental Observations. By Evan Calkins (by invitation), George W. Dana (by invitation), J. C. Seed (by invitation) and John Eager Howard.

2. Nor-Epinephrine in Adrenal Medulla. By Marcel Goldenberg and Mogens Faber (introduced by R. F. Loeb).

3. Studies on an Anti-Diuretic, Non Chloruretic Substance Extracted from Urines of Normal and Cirrhotic Subjects. By Elaine P. Ralli, Stephen Leslie (by invitation), George H. Stueck, Jr. (by invitation) Mary E. Dumm and Bertram Laken (by invitation).

4. A Method for the Assay of Prolactin in Human Urine. By Richard L. Coppedge (by invitation) and Albert Segaloff.

5. Thyrotrophic and Thyroid Hormone Assay of Normal and Pathologic Human Sera in the Stasis Tadpole. By S. A. D'Angelo, A. S. Gordon, K. E. Paschkis and A. Cantarow.

6. Estimation of Urinary Gonadotrophin of the Non-pregnant Human by the Mouse Uterine Weight and Ovarian Hyperemia Responses. By Charles W. Lloyd, Muriel Morley (by invitation), Kathryn Morrow (by invitation), Julia Lobotsky (by invitation) and Edward C. Hughes (by invitation).

7. Further Studies of Antigonadotrophin Formation in Man. By James H. Leathem and A. E. Rakoff.

8. The Evaluation of the Use of Anterior Pituitary Extract in the Treatment of Pituitary Dwarfism. By Joseph C. Edwards, Cecil M. Charles (by invitation) and Cyril M. MacBryde.

9. On the Inability of Adrenocorticotrophic Hormone or Epinephrine to Deplete the Ascorbic Acid of the Chick Adrenal. By Norman F. Boas (by invitation) and Joseph W. Jailer.

10. Regulation of Pituitary Adrenocorticotrophic Activity by Adrenal Cortical Hormones. By Chi-Ping Cheng (introduced by George Sayers).

11. Adequacy of Pituitary Adrenocorticotrophic Function in Nutritional Deficiencies. By George Sayers.

12. Effects of Prolonged Adrenal Cortical Stimulation upon Free and Esterified Serum Cholesterol in Normal Men. By Jerome W. Conn and William C. Vogel (by invitation).

13. Possible Involvement of the Adrenal Cortex and Thyroid in Mobilization of Fat to the Liver. By Louis Levin.

FRIDAY, JUNE 3, 1949

2:00 p.m.—J. S. L. Browne, presiding

14. Stimulation of Nitrogen by Adrenal Cortical Extract during Insulin Hypoglycemia. By Frank L. Engel.

15. Renal Function in Normal and Adrenalectomized Rats following Saline or Adrenal Steroid Administration. By W. R. Boss (by invitation) James H. Birine and Robert Gaunt.

16. Adrenal Cortical Hormone in Blood. By K. E. Paschkis, A. Cantarow and D. Boyle (by invitation).

17. Urinary Corticoids. By Eleanor H. Venning, M. P. Ripstein (by invitation) and V. E. Kazmin (by invitation).

18. Studies on the Interrelationship of Adrenal and Thyroid Function. By Robert S. Reiss, Peter H. Forsham (by invitation) and George W. Thorn.

19. Clinical and Metabolic Changes in Addison's Disease Following the Administration of Compound E Acetate (11-dehydro, 17-hydroxy-corticosterone acetate). By P. H. Forsham (by invitation), L. L. Bennett (by invitation), M. Roche (by invitation), R. S. Reiss, A. Slessor (by invitation), E. B. Flink (by invitation) and G. W. Thorn.

20. Effect of a Single Dose of Desoxycorticosterone Acetate on Electrolyte Metabo-

lism. By Paul Fourman (by invitation), Edwin J. Kepler, Edward C. Reifenstein, Jr. and Eleanor F. Dempsey (by invitation).

21. Changes in Urinary Steroids Produced by Sodium Deprivation and by Desoxycorticosterone Acetate Administration. By William H. Daughaday (by invitation) and Cyril M. MacBryde.

22. The Evaluation of Adrenocortical Function by Ascertaining the Reponse to a Single Injection of Adrenocorticotrophin. By H. W. McIntosh (by invitation), B. Singer (by invitation) and M. M. Hoffman.

23. The Level of Circulating Eosinophils as an Indicator of Adrenal Cortical Adequacy Following Major Surgery. By Marcel Roche (by invitation), A. Gorman Hills (by invitation) and George W. Thorn.

24. Is the Protein Metabolic Abnormality of Cushing's Syndrome Catabolic or Anti-Anabolic? By Sheldon Margen (by invitation), Laurence W. Kinsell, Erin K. Flanagan (by invitation), Lila E. Suiter (by invitation) and Elliot Rapaport (by invitation).

25. Hypokaliemic Alkalosis in Cushing's Syndrome. Observations on the Effects of Potassium Chloride and Testosterone Proprionate Therapy. By Robert Teabeaut (by invitation), Frank L. Engel and Haywood M. Taylor (by invitation).

26. The Mechanism of Action of Testosterone in the Therapy of Cushing's Syndrome. By Frederick C. Bartter (by invitation), Anne P. Forbes, William M. Jefferies, Evelyn L. Carroll (by invitation) and Fuller Albright.

SATURDAY, JUNE 4, 1949

9:00 a.m.—E. A. Doisy, presiding

27. Metabolism and Distribution of Thiourea in the Rat as measured with Radioactive Sulfur. By John Schulman, Jr. and Richard P. Keating (introduced by Rulon W. Rawson).

28. The Tracer Technique with Radioiodine I^{131} as a Potential Substitute for the Basal Metabolic Rate Determination in Routine Clinical Practice. By Sidney C. Werner.

29. The Distribution and Metabolism of Circulating Testosterone. By C. D. West and L. T. Samuels.

30. Pseudo-hypoparathyroidism: A Report of Two New Cases with Special Reference to the Epiphyseal Changes. By Harold Elrick (by invitation), Frederic C. Bartter (by invitation), Adney Sutphin (by invitation) and Fuller Albright.

31. Quantitative Measurements of the Growth of Axillary Hair as an Index of the Endocrine Status. By James B. Hamilton.

32. The Effects of Testosterone Propionate on the Peripheral Blood and Bone Marrow of Women with Advanced Carcinoma of the Breast. By Timothy R. Talbot, Jr. (by invitation) and George C. Escher.

33. Effects of Small Doses of Testosterone Propionate on Spermatogenesis. By Cleve Beller (by invitation) and Henry H. Turner.

34. Endocrine Factors in Gout: The Significance of Differences in Childhood and Adult Urate Metabolism. By William Q. Wolfson, David Krevsky, Rachmiel Levine (by invitation), Kinu Kadota (by invitation) and Clarence Cohn.

35. The Effect of Castration, of Unilateral Castration and of Pregnancy in Unilaterally Castrate Rats on the Ovary Transplanted into the Spleen. By Gerson R. Biskind and Morton S. Biskind.

36. The Occurrence of Conjugated Sulfates of Estrogens in Human Pregnancy Urine. By Herman Cohen (by invitation) and Robert W. Bates.

37. Hormonal Factors Producing the Gametokinetic Response in the Male Frog (Rana Pipiens). By Robert B. Greenblatt, Sarah Clark (by invitation) and R. M. West (by invitation).

38. Action of Estrogens on Release of Luteinizing Hormone in Menopausal Women. By Arthur A. Hellbaum, J. W. Funnell (by invitation) and E. C. Keaty (by invitation).

39. The Hormonal Pattern in Pseudocyesis. By A. E. Rakoff and Paul H. Fried (by invitation).

40. Management of Threatened Abortion in the Human with Large Doses of Prethylstilbestrol. By A. B. Abarbanel.

SATURDAY, JUNE 4, 1949

2:00 p.m.—C. H. Best, presiding

Joint Meeting with The American Diabetes Association

41. A Hyperglycemic Factor Extracted from the Pancreas. 10 mins. By I. J. Pincus (introduced by A. E. Rakoff).

42. Studies in Carbohydrate Metabolism in Decerebrate Rats. 10 mins. By Evelyn Anderson and Webb Haymaker (by invitation).

43. Factors Affecting the Volume of the Islands of Langerhans. 15 mins. By R. E. Haist, Margaret Evans and B. Kinash (introduced by C. H. Best).

44. Studies on the Serum Potassium in Diabetic Acidosis. 15 mins. By Carl S. Nadler, Samuel Bellett and Mary Lanning (introduced by C. H. Best).

45. Pyruvic and Citric Acid Metabolism. 15 mins. By Max Miller and Ernest Bueding (introduced by C. H. Best).

46. Changes in Inorganic Serum Phosphorus during the Intravenous Glucose Tolerance Test as an Adjunct to the Diagnosis of Early Diabetes Mellitus. 15 mins. By Peter H. Forsham (by invitation), Marcel Roche (by invitation) and G. W. Thorn.

47. The Metabolism of Glucose and Galactose when Administered Simultaneously to Man. 10 mins. By G. C. Walsh (by invitation), M. M. Hoffman, H. T. McAlpine (by invitation) and E. H. Mason (by invitation).

48. Studies in Fat Metabolism. 1. Steroid Hormonal Effects Upon Blood Ketones and Other Intermediate Products of Fat and Protein Catabolism. 10 mins. By Laurance W. Kinsell, Sheldon Margen (by invitation), George D. Michaels (by invitation), Betty T. Signorotti (by invitation) and David P. McCallie (by invitation).

49. The Urinary Excretion of Corticosteroids in Diabetic Acidosis. 10 mins. By Janet W. McArthur, Randall G. Sprague and Harold L. Mason.

50. Steroid Diabetes Associated with Cushing's Syndrome and Excretion of 17-Hydroxycorticosterone (Compound F) in Urine; Metabolic Studies. 10 mins. By Randall G. Sprague, Alvin B. Hayles (by invitation), Harold L. Mason, Marschelle H. Power (by invitation) and Warren A. Bennett (by invitation).

51. Behavior of Electrolytes During Treatment of Diabetic Keto-Acidosis. 10 mins. By Jonas Weissberg, (by invitation), Thomas H. McGavack, A. M. Shearman (by invitation) and I. J. Drekter.

TO BE READ BY TITLE

52. Correlation of Vaginal Smears and Endometrial Biopsies in Normal Cycles and in Gynecic Disorders. By H. E. Nieburgs, Robert B. Greenblatt and S. Bamford (by invitation).

53. The Effect of Pteroylglutamic Acid Antagonists on the Response of the Reproductive Accessories of C57 Male Mice to Testosterone. By E. D. Goldsmith, H. M. Black (by invitation) and R. F. Nigrelli (by invitation).

54. Synthesis of Testosterone from Androstenedione-3, 17 by Testis Tissue. By Leo T. Samuels, Blaine H. Levedahl (by invitation), M. L. Helmreich (by invitation) and M. M. Pottner (by invitation).

55. The Role of the Adrenal Cortex in Some Somato-Sexual Aberrations in Infants and Children. By M. M. Melicow.

56. Effects of Compound E on Blood Ketone Bodies. By Leslie L. Bennett (by invitation), Alexander Slessor (by invitation) and George W. Thorn.

57. The Effect of Dietary Protein on the Ability of the Liver to Inactivate Estradiol in the Rat. By Joseph W. Jailer.

58. Pregnanediol Excretion in Cases of Blighted Ovum. By A. B. Abarbanel, Robert Hoyt (by invitation) and M. G. Levine (by invitation).

59. A Mechanism of Potassium Deficiency in Alkalosis. By Charles H. Burnett, Belton A. Burrows (by invitation) and Robert R. Commons (by invitation).

60. Effects of Hemopoietic Agents on Blood Formation in Hypophysectomized Rats. By Robert Gerstner (by invitation) and Albert S. Gordon.

61. The Relative Effectiveness of Desoxycorticosterone Acetate in Oil Solution and in Pellets Diluted with Cholesterol. By Albert Segaloff.

62. Adrenal Cortex Activity in Essential Hypertension. By Louis Tobian, Jr. and Harold Joseph (introduced by Carl A. Bunde).

63. The White Blood Cell Response of Rats to Adrenalectomy, Stress, and Pantothenic Acid. By Mary E. Dumm, Paul Roth (by invitation), Paul Ovando (by invitation) and Elaine P. Ralli.

64. Role of Emotional Stress in the Survival of Adrenalectomized Rats given Replacement Therapy. By Miguel R. Covian (introduced by Curt Richter).

65. The Androgenic Activity of New Esters of Testosterone. By A. J. Bergmann and Lloyd C. Miller (introduced by John S. L. Browne).

66. Effect of Androgen and Growth Hormone on the Rat's Os Penis. By Wm. R. Lyons, Edward Abernethy (by invitation) and Mark Grooper (by invitation).

67. The "Thiocyanate Space" and "Iodide Space" in the Thyroid Gland. By J. F. McClendon, William C. Foster (by invitation) and Emerson Reed (by invitation).

68. A Comparison of the 17-Ketosteroid Excretion of Cases of Cushing's Syndrome Due to Adrenal Tumor with Those Due to Hyperplasia (Hyperfunction). By Anne P. Forbes, Evelyn L. Carroll (by invitation) and Mary L. Wheeler (by invitation).

69. Sex Hormones and Staphylococcus Infections. By Manuel Villaverde.

70. The Problem of Allergy to Steroid Hormones. By George P. Heckel.

71. Intravenous Estrogen in Menometrorrhagia in the Human. By A. R. Abarbanel.

72. The Incidence of Cancer in Endocrine Case Histories. By J. K. Fancher and Jean Brooks (by invitation).

73. Renal Clearances in Patients with Cirrhosis of the Liver, with and without Ascites. By Stephen H. Leslie, Barbara Johnson (by invitation) and Elaine P. Ralli.

74. Porphyria Simulating Anorexia Nervosa. By Bernard A. Watson.

75. Hemosedimentation Test in Obesity. Aulo Pinto Viégas.

76. The Effects of Vitamin B, Thyroid, and Adrenal Alterations on the Amino Acid Oxidase Activity of Rat Liver and Kidney. By Samuel R. Tipton and Frances M. Colvin (by invitation).

77. The Problem of Endemic Goiter in Yunnan Province. By Isidor Greenwald.

The 1949 Annual Meeting of the American Diabetes Association

CHALFONTE-HADDON HALL,

ATLANTIC CITY, N. J.

SATURDAY AFTERNOON, JUNE 4; Joint Meeting with the Association for the Study of Internal Secretions.

SUNDAY MORNING AND AFTERNOON, JUNE 5.

BANQUET, SATURDAY NIGHT.

Please send reservations for the banquet now to this office. Wives of members are welcome. Dinner subscriptions—$6.00—*Payable when you register* at the meeting.

Postgraduate Course in Endocrinology, Including Diabetes

THE MEDICAL CENTER, UNIVERSITY OF CALIFORNIA MEDICAL SCHOOL

Parnassus and Third Avenues, San Francisco 22, California

JUNE 20 THROUGH 24, 1949

TOLAND HALL, UNIVERSITY OF CALIFORNIA HOSPITAL

General Chairman of Course: Hans Lisser, M.D., Clinical Professor of Medicine, University of California Medical School.

Chairman of Program: Roberto F. Escamilla, M.D., Associate Clinical Professor of Medicine, University of California Medical School.

Officers of Instruction:

Drs. T. L. Althausen, H. G. Bell, R. C. Benson, L. S. Craig, M. E. Dailey, W. C. Deamer, R. F. Escamilla, M. B. Goldberg, L. Goldman, G. S. Gordan, Jr., J. B. Graham, J. O. Haman, F. Hinman, F. Hinman, Jr., W. J. Kerr, L. W. Kinsell, H. Lisser, B. V. A. Low-Beer, H. J. McCorkle, E. P. McCullagh, E. R. Miller, H. C. Naffziger, M. B. Olney, A. Palmer, H. H. Searls, H. C. Shepardson, F. S. Smyth, R. S. Stone, R. Ward, H. M. Weyrauch and A. Zeibak.

This course is open only to graduates of medical schools approved by the Council on Medical Education and Hospitals of the American Medical Association.

The fee for the course is $50.00, payable at the time of enrollment, either by check or money order made payable to THE REGENTS OF THE UNIVERSITY OF CALIFORNIA. Please indicate the course for which application is being made.

University Extension reserves the right to cancel this course, in which case all fees will be refunded.

Application is to be made to: Stacy R. Mettier, M.D., Head of Postgraduate Instruction, Medical Extension, University of California Medical Center, San Francisco 22, California. Telephone: MOntrose 4-3600, local 255.

VETERANS

Those applying for educational benefits under federal or state statutes will present, at the time of registration, their Certificates of Eligibility and Entitlement which will be accepted in lieu of the fee. Veterans who previously have filed their Certificates with University Extension and have not used their educational benefits elsewhere in the interim will likewise be admitted without fee, provided they have sufficient credit left on their Certificates. Application for the Certificate of Eligibility and Entitlement may be made through local offices of the Veterans Administration, and *must be dated prior to the beginning of the course.*

Books Received

THE following list acknowledges receipt of books which it has not been possible for us to review as yet:

La Citologia Vaginal Humana en Condiciones Normales y Patalógicas. By INÉS L. C. DE ALLENDE, Doctora en Medicina, Jefe de la Sección Endocrinologia del Instituto de Investigación Médica, Córdoba, Argentina, and OSCAR ORÍAS, Doctor en Medicina, Director del Instituto de Investigación Médica, Córdoba, Argentina. Prólogo del Prof. Dr. BERNARDO A. HOUSSAY. 313 pages. 105 illustrations (53 in color). 1947. El Ateneo, Buenos Aires, Argentina.

Clinical Endocrinology and Constitutional Medicine. By A. P. CAWADIAS, O.B.E., M.D., F.R.C.P., Endocrinologist to the Order of St. John Clinic. 368 pages. 14 illustrations. 1947. Frederick Muller, Ltd., London, England. Price 42'-net.

Crystalline Enzymes. 2nd Ed. revised and enlarged. By JOHN H. NORTHROP, Member, The Rockefeller Institute for Medical Research, Princeton, New Jersey, and sharer of the Nobel Prize in Chemistry for 1946; MOSES KUNITZ, Associate Member, The Rockefeller Institute for Medical Research, and ROGER M. HERRIOTT, Associate, The Rockefeller Institute for Medical Research. 352 pages. 105 illustrations. 1948. Columbia University Press, New York. Price $7.50.

Los Desordenes de la Menstruacion y su Tratamiento: Base Experimental de la Interrelación Prehipófiso-ovárica. By DR. EMILIO COLOMBO. 327 pages. 159 figures. 1949. El Ateneo, Buenos Aires.

Diabetes and its Treatment. By JOSEPH H. BARACH, M.D., F.A.C.P., Associate Professor of Medicine, University of Pittsburgh; Senior Medical Staff, Presbyterian Hospital; Medical Director, Outpatient Department of the Medical Center Hospitals; School of Medicine, University of Pittsburgh. 326 pages. 73 illustrations. 1949. Oxford University Press, New York. Price $10.00.

The Diabetic's Handbook. By ANTHONY SINDONI, JR., M.D., Chief of the Department of Metabolism, Philadelphia General and St. Joseph Hospitals; Chairman of the Advisory Committee on Diabetes to the Director of the Department of Public Health, Philadelphia; Chief of the Diseases of the Metabolism, St. Francis Hospital, Wilmington, Delaware. 194 pages. 7 illustrations. 1948. The Ronald Press Company, New York. Price, $3.00.

Diagnosis and Treatment of Menstrual Disorders and Sterility. 2nd Ed. revised and enlarged. By CHARLES MAZER, M.D., F.A.C.S., Assistant Professor of Gynecology and Obstetrics, Graduate School of Medicine, University of Pennsylvania; Gynecologist to the Mount Sinai Hospital, Philadelphia, and S. LEON ISRAEL, M.D., F.A.C.S., Instructor in Gynecology and Obstetrics, School of Medicine, University of Pennsylvania; Associate Gynecologist to the Mount Sinai Hospital, Philadelphia. 570 pages. 133 illustrations. 1946. Paul B. Hoeber, Inc., New York. Price, $7.50.

Diagnosis in Sterility. 1st Ed., 2nd printing. Proceedings of the Conference on Sterility, sponsored by the National Committee on Material Health. Edited by EARL T. ENGLE, College of Physicians and Surgeons, New York. 237 pages. 30 illustrations. 1947. Charles C Thomas · Publisher, Springfield, Illinois. Price $5.50.

Diagnostic Hormonal et Traitements Hormonaux en Gynécologie. By CLAUDE BÈCLÉRE. Préface by Professeur H. SIMONNET. 373 pages. 1946. Masson et C^{ie}, Paris. Price 525 fr.

Diseases of the Adrenals. 2nd Ed. By LOUIS J. SOFFER, M.D., Associate Attending Physician, The Mount Sinai Hospital, New York City; Assistant Clinical Professor of Medicine, Columbia University, New York. 320 pages. 45 illustrations (3 color plates). 1948. Lea & Febiger, Philadelphia. Price $6.50.

Endocrine Function of the Hypophysis. By HARRY B. FRIEDGOOD, M.D., Assistant Clinical Professor of Medicine, University of Southern California and Senior Attending Physician, Los Angeles County Hospital, Los Angeles, California. Edited by HENRY A. CHRISTIAN, A.M., M.D., LL.D., Sc.D(Hon.), F.A.C.P., Hon. F.R.C.P. (Can.), Hersey Professor of the Theory and Practice of Physics, Emeritus, Harvard University; Clinical Professor of Medicine, Tufts Medical Physician-in-Chief, Emeritus, Peter Bent Brigham Hospital; Visiting Physician, Beth Israel Hospital, Boston, Massachusetts. (Reprinted from Oxford Loose-Leaf Medicine, with the same page numbers as in that work). 240 pages. 36 illustrations. 1946. Oxford University Press, New York.

Endogeneous Endocrinotherapy Including The Causal Cure of Cancer. (Compendium) By DR. JULES SAMUELS, Specialist for endogeneous endocrinotherapy, Amsterdam. 539 pages. 30 illustrations. 1947. Holdert & Co., Amsterdam.

Essai de Physiopathologie Thyro-Hypophysaire. By Dr. JACQUES MAHAUX, Agrégé de l'enseignement supérieur, Adjoint de la Clinique médicale universitaire (Belgique). Préface du Professeur E. J. BIGWOOD. 268 pages. 29 figures. 1947. Masson et C^{ie}, Paris. Price 530 fr.

Essentials of Endocrinology. 2nd Ed. revised and enlarged. By ARTHUR GROLLMAN, Ph.D., M.D., F.A.C.P. Professor of Medicine, The Southwestern Medical College; Attending Physician and Consultant in Endocrinology. The Parkland Hospital, Dallas, Texas. 644 pages. 132 illustrations. 1947. J. B. Lippincott Company, Philadelphia.

Essentials of Gynecologic Endocrinology. By GARDNER M. RILEY, Ph.D., Assistant Professor of Obstetrics and Gynecology, University of Michigan Medical School. 205 pages. 35 figures and 1 color plate. 1948. Caduceus Press, Ann Arbor, Michigan.

Experimental Immunochemistry. By ELVIN A. KABAT, Ph.D., Associate Professor of Bacteriology, College of Physicians and Surgeons, Columbia University and the Neurological Institute, New York; and MANFRED M. MAYER, Ph.D., Associate Professor of Bacteriology, School of Hygiene and Public Health, The Johns Hopkins University, Baltimore, Maryland. With a foreword by MICHAEL HEIDELBERGER, Ph.D., Professor of Biochemistry, College of Physicians and Surgeons, Columbia University, and Chemist to the Presbyterian Hospital, New York. 575 pages. 88 illustrations. 1948. Charles C Thomas · Publisher, Springfield, Illinois. Price $8.75.

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General Endocrinology. By C. DONNELL TURNER, Ph.D., Associate Professor of Zoology at Northwestern University. 604 pages. 164 illustrations. 1948. W. B. Saunders Company, Philadelphia.

Hormones and Behavior—A Survey of Interrelationships Between Endocrine Secretions and Patterns of Overt Response. By FRANK A. BEACH, Professor of Psychology, Yale University. With a foreword by EARL T. ENGLE, M.D., College of Physicians and Surgeons, Columbia University, New York. 368 pages. 1948. Paul B. Hoeber, Inc., New York and London. Price $6.50.

L'Hyperfolliculine—Étude Clinique, Anatomo-Pathologique et Thérapeutique. By MAX WALLET. Preface by L. de GENNES. 354 pages. 25 figures. 1946. Masson et C^{ie}, Paris. Price 480 fr.

The Modern Treatment of Diabetes Mellitus, Including Practical Procedures and Precautionary Measures. By WILLIAM S. COLLENS, B.S., M.D., Chief of the Diabetic Clinic, and of the Clinic for Peripheral Vascular Diseases and Associate Visiting Physician, Israel Zion Hospital, Brooklyn; Associate Visiting Physician, Greenpoint Hospital, Brooklyn; Attending Metabolist, Jewish Sanitarium and Hospital for Chronic Diseases, Brooklyn; and LOUIS C. BOAS, A.B., M.D., Assistant in the Diabetic Clinic and in the Clinic for Peripheral Vascular Diseases, Israel Zion Hospital, Brooklyn; Chief of the Diabetic Clinic and Assistant Visiting Physician, Greenpoint Hospital, Brooklyn; Associate in Department of Metabolism, Jewish Sanitarium and Hospital for Chronic Diseases, Brooklyn, New York. 514 pages. 193 illustrations. 1946. Charles C Thomas · Publisher, Springfield, Illinois. Price $8.50.

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Natural Products Related to Phenanthrene. 3rd Ed. By LOUIS F. FIESER and MARY FIESER, Department of Chemistry, Harvard University. 704 pages. 1949. Reinhold Publishing Corporation, New York. Price $10.00.

Office Endocrinology. 3rd Ed. Revised and enlarged. By ROBERT B. GREENBLATT, B.A., M.D., C.M., Professor of Endocrinology, University of Georgia School of Medicine; Director, Sex Endocrine Clinic, University Hospital, Augusta, Georgia. With a foreword by G. LOMBARD KELLY, M.D., Dean, University of Georgia School of Medicine. 306 pages. 71 figures. 1947. Charles C Thomas · Publisher, Springfield, Illinois. Price $4.75.

Pathology and Surgery of Thyroid Disease. By JOSEPH L. DECOURCY, M.D., Senior Surgeon, Good Samaritan Hospital; Director, DeCourcy Clinic, Cleveland, Ohio, and CORNELIUS B. DECOURCY, M.D., Member DeCourcy Clinic Surgical Staff, Cincinnati, Ohio. 476 pages. 94 illustrations (4 in color). 1949. Charles C Thomas · Publisher, Springfield, Illinois.

Practical Aspects of Thyroid Disease. By GEORGE CRILE, JR., M.D., F.A.C.S., Department of Surgery, Cleveland Clinic. 354 pages. 101 illustrations. 1949. W. B. Saunders Company, Philadelphia.

Practical Office Gynecology. By KARL JOHN KARNAKY, M.D., Assistant Professor of Clinical Gynecology, Baylor University College of Medicine; Gynecologist to Jefferson Davis Hospital, Houston, Texas. 261 pages. 113 figures showing 238 illustrations; 29 figures are in color, showing 73 illustrations. 1947. Charles C Thomas · Publisher, Springfield, Illinois. Price $7.50.

The Practice of Endocrinology. Edited by RAYMOND GREENE, M.A., D. M., M.R.C.P. with contributions by A. C. CROOKE, M.A., M.D., Clinical Endocrinologist Birmingham United Hospital, the Birmingham and Midland Hospitals for Women, and the Children's Hospital, Birmingham, England; DONALD HUNTER, M.D., F.R.C.P., London Hospital; R. D. LAWRENCE, M.A., M.D., Physician in charge of the Diabetic Department of King's College Hospital, London; J. M. ROBSON, M.D., D.Sc., F.R.S.E., reader in Pharmacology at Guy's Hospital Medical School, London; F. F. RUNDLE, M.D., F.R.C.S., Assistant Surgeon and Assistant Director of the Surgical Professorial Unit at St. Bartholomew's Hospital, London; Rockefeller Travelling Fellow; formerly Hunterian Professor, Royal College of Surgeons, London; and P. H. SANDIFIER, M.R.C.P., of the Maida Vale Hospital for Nervous Diseases; Neurological Physician Royal National Orthopaedic Hospital, London. 366 pages. 19 figures and 53 plates (1 colored). 1948. Eyre & Spottiswoode, London, England. Price 52s. 6d.

Pregnancy Diagnosis Tests: A Review. By ALFRED T. COWIE, B.Sc., M.R.C.V.S., Ph.D., National Institute for Research in Dairying, University of Reading. 283 pages. 1948, Joint Publication No. 13 Commonwealth Agriculture Bureaux, Penglais, Aberystwyth, Great Britain. Price 15s.

Psychodynamics and the Allergic Patient. By HAROLD A. ABRAMSON, M.D., F.A., F.A.C.A., Associate Physician for Allergy, The Mount Sinai Hospital, New York, New York; Consulting Physician for Allergy, Sea View Hospital, Staten Island, New York; Assistant Professor of Physiology, Columbia University, New York. 81 pages. 1948. The Bruce Publishing Company, St. Paul and Minneapolis.

Recent Advances in Endocrinology. 6th Ed. By A. T. CAMERON, C.M.G., M.A., D.Sc. (Edin.) F.R.I.C., F.R.S.C., Professor of Biochemistry, University of Manitoba, and Biochemist at the Winnipeg General Hospital, Winnipeg, Canada. 443 pages. 74 illustrations. 1947. The Blakiston Company, Philadelphia and Toronto. Price $6.00.

On the Relation Between the Thyroid Gland and Uterine Myoma. By MAURI ROUHUNKOSKI. 83 pages. 1948. Mercatorin Kirkapaino, Helsinki.

The Renal Origin of Hypertension. By HARRY GOLDBLATT, M.D., C.M., Director, Institute for Medical Research, Cedars of Lebanon Hospital; Professor of Pathology, University of Southern California, Los Angeles, California. A monograph in American Lectures in Pathology, edited by PAUL R. CANNON. 126 pages. 38 illustrations.1948. Charles C Thomas · Publisher, Springfield, Illinois. Price $2.75.

Sexual Endocrinology of Non-Mammalian Vertebrates. By L. H. BRETSCHNEIDER and J. J. DUYVENE DE WIT, from the laboratory for General Zoology, University of Utrecht, Netherlands. Number 11 in Monographs on the Progress of Research in Holland During the War. 146 pages. 96 illustrations. 1947. Elsevier Publishing Company, Inc., New York. Price $2.75.

Sterility and Impaired Fertility. Pathogenesis, Investigation and Treatment. 2nd Ed. By CEDRIC LANE-ROBERTS, C.V.O., M.S., F.R.C.S., F.R.C.O.G., Gynaecological Surgeon Royal Northern Hospital, Consulting Obstetric Surgeon, Queen Charlotte's Hospital; ALBERT SHARMAN, M.D., Ph.D., M.R.C.O.G., Senior Assistant Surgeon, Royal Samaritan Hospital for Women, Glasgow, Assistant Lecturer in Clinical Gynaecology, University of Glasgow; KENNETH WALKER, M.A., M.B., B.C. (Cantab), F.R.C.S., F.I.C.S., Jacksonian Prizeman and Hunterian Professor, Royal College of Surgeons, Emeritus Surgeon, Royal Northern Hospital, Andrologist, Philip Hill Parenthood Clinic; B. P. WIESNER, D.Sc., Ph.D., F.R.S.E., Consulting Biologist, Royal Northern Hospital; and MARY BARTON, M.B., B.S., First Assistant to the Fertility Clinic, Royal Free Hospital, London. 400 pages. 96 illustrations. 1948. Paul B. Hoeber, Inc., New York.

Temporary Rise in the Frequency of Thyrotoxicosis in Denmark 1941–1945. By KURT IVERSEN. Translated from the Danish by Hans Andersen, M.D. 244 pages. 1948. Rosenkilde and Bagger, Copenhagen.

Traité de Neuro Endocrinologie. Le Système Neuro-Endocrinien, le Complexe Hypothalamo-Hypophysaire, la Neuro-Ergonologie, et son Evolution Récente. By GUSTAVE ROUSSY and MICHEL MOSINGER. 1106 pages. 261 figures. 1946. Masson et Cie, Paris. Price 2200 fr.

Tuberculosis of the Knee Joint. By JOHANNES MORTENS. Translated from the Danish by AXEL ANDERSEN. 550 pages. 1948. Einar Munksgaard, Copenhagen, and K. H. Lewis & Co. Ltd., London.

Die Weiblichen Sexualhormone in der Pharmakotherapie. By Dr. Med. O. MÜHLBOCK, Amsterdam. Prof. Dr. Med. H. KNAUS, Graz; and Doz. Dr. Med. E. TSCHERNE, Graz. 300 pages. 43 illustrations (4 in color). 1948. Medizinischer Verlag Hans Huber, Bern. Distributed in U.S.A. and Canada by Grune & Stratton, Inc., New York.

Abstracts of

CURRENT ENDOCRINE LITERATURE

Editor: ROY HERTZ. *Collaborators:* A. R. ABARBANEL, F. N. ANDREWS, B. L. BAKER, F. A. DE LA BALZE, ISRAEL BRAM, R. A. CLEGHORN, RUCKER CLEVELAND, C. D. DAVIS, ANNA FORBES, M. B. GORDON, H. S. GUTTERMAN, M. M. HOFFMAN, R. G. HOSKINS, C. D. KOCHAKIAN, H. S. KUPPERMAN, H. L. MASON, JANET W. MCARTHUR, THOMAS H. MCGAVACK, A. E. MEYER, K. E. PASCHKIS, A. B. PINTO, J. R. REFORZOMEMBRIVES, E. C. REIFENSTEIN, JR., G. G. RUDOLPH, L. T. SAMUELS.

ADRENALS

GREEN, D. M.: Mechanisms of desoxycorticosterone action. I. Relation of fluid intake to blood pressure, *J. Lab. & Clin. Med.* **33**: 853–859, 1948.

Since the results of preliminary investigations suggested that desoxycorticosterone (DCA) may possess the ability to elevate mean pressure without production of secondary cardiac slowing or pulse pressure increase, studies were made of the mechanisms by which this drug affects the height of the blood pressure level. Implantation of a single 20 mg. pellet of DCA in young rats maintained on isotonic saline solution was followed immediately by a rise on fluid intake, later by a secondary regression of intake values toward control levels and the reciprocal development of hypertension. The degree of this hypertension appeared to be in proportion to the dosage of the drug, the maximal rise in fluid intake, and the subsequent rate of decline in intake. Adrenalectomy apparently did not sensitize the test animals to the actions of DCA. The author suggests that the hypertension induced by overdosage of DCA may not represent a direct action, but may be a compensatory mechanism for overcoming distortions in fluid and electrolyte balance produced by the drug.—T.H.McG.

LA DUE, J. S.; MURISON, P. J., and PACK, G. T.: The use of tetraethylammonium bromide as a diagnostic test for pheochromocytoma, *Ann. Int. Med.* **29**: 914–921, 1948.

The responses of a patient with pheochromocytoma to the parenteral administration of histamine diphosphate and of tetraethylammonium bromide are presented. Both agents induced a paroxysm of severe hypertension. However, that following the administration of histamine was uncontrollable, whereas the level and duration of blood pressure rise after the administration of tetraethylammonium bromide could be controlled by a change in the patient's posture.—*J.M.*

MASON, H. L., and SPRAGUE, R. G.: Isolation of 17-hydroxycorticosterone from the urine in a case of Cushing's syndrome associated with severe diabetes mellitus, *J. Biol. Chem.* **175**: 451–56, 1948.

In this case of Cushing's syndrome, associated with bilateral hyperplasia of the adrenal cortex, 191 mg. of 17-hydroxycorticosterone was isolated from the urine collected during a 25-day period. The total corticosteroids excreted, as measured by a chemical procedure, was 14 to 19 mg. per day. Isolation of this adrenal cortical hormone, which is the most active one known with respect to carbohydrate metabolism, supports the view that at least some of the manifestations of Cushing's syndrome are primarily the result of an overproduction of those cortical hormones which are active in carbohydate metabol-

ism. The presence of severe diabetes which was refractory to insulin was analogous to the insulin-resistant hyperglycemia and glycosuria induced in rats by administration of the carbohydrate-active cortical hormones.—*H.L.M.*

SELYE, H.: The alarm reaction and the diseases of adaptation, *Ann. Int. Med.* **29**: 403–415, 1948.

The author reviews the principal observations upon which the concept of "diseases of adaptation" is based, with special reference to nephrosclerosis and hypertension. The pathogenicity of mineralocorticoids produced in response to stress can apparently be modified by several metabolic factors. Diets poor in sodium and protein and treatment with acidifying salts tend to prevent experimentally-induced nephrosclerosis and hypertension. The application of these observations to clinical medicine is briefly discussed.—*J.M.*

GONADS

ABARBANEL, A. R.: Artificial reproduction of the cyclic changes in cervical mucus in human castrates: with clinical correlations, *West. J. Surg.* **56**: 26–34, 1948.

By the administration of estrogens to female castrates (with a stump of cervix remaining) it was possible to duplicate the alteration in the cervical mucus characteristic of the immediate pre-ovulatory or co-ovulatory phase of the cycle. These alterations consist of a decided increase in the volume of cervical secretions, a marked decrease in viscosity and almost complete absence of polymorphonuclear leukocytes. This clear watery mucus is rapidly penetrable by relatively large numbers of sperm which remain actively motile in it for 24 to 72 hours, a longer time by far than in mucus obtained at any other time in the cycle. In control castrates progesterone alone, as well as testosterone preparations, were not observed to stimulate the flow of cervical mucus.—*J.M.*

FRIED, P. H.: The two hour pregnancy test, based on rat ovary hyperemia, *West. J. Surg.* **56**: 552–555, 1948.

The rat hyperemia test was performed by the author on specimens obtained from 500 pregnant and nonpregnant patients, with an over-all accuracy of 96.8 per cent. The advantages cited for the test, as compared to the conventional methods, are its increased sensitivity and rapidity, the scarcity of false positive reactions, the increased tolerance of the rat to toxic specimens of urine and the convenience of the test and test animals. Disadvantages are the false negative reactions and the lack of a sharp positive endpoint.—*J.M.*

GUTERMAN, H. S., and SCHROEDER, M. S.: A simplified technique for the quantitative colorimetric estimation of pregnandiol in urine, *J. Lab. & Clin. Med.* **33**: 356–366, 1948.

In contrast to the majority of quantitative methods for estimation of urinary pregnandiol, the colorimetric procedure described requires only small amounts of urine, manipulation is technically simple, and no special apparatus and chemicals are needed. The quantitative determination of pregnandiol in a given specimen of urine depends on its spectrophotometric absorption at 430 millimicra. The estimation of pregnandiol alone is possible with this method; androsterone does not interfere with the color reaction. Results of determinations in the menstrual cycle and in pregnancy check closely with those obtained with the longer gravimetric procedure as observed in other laboratories.—*T.H.Mc.G.*

SEVRINGHAUS, E. L.: Use of estrogens in medicine, *Ann. Int. Med.* **29**: 595–600, 1948.

The physiologic actions of the estrogens and possible modes and routes of administration are briefly reviewed. The utilization of estrogenic therapy in the menopausal syndrome, dysmenorrhea, and adolescent hypoplasia of the breasts or uterus is discussed. Absolute and relative contraindications to the use of estrogens are considered.—*J.M.*

TYLER, E. T.; PAYNE, S., and KIRSCH, H.: Pregnenolone in male infertility, *West. J. Surg.* **56**: 459–463, 1948.

Pregnenolone was administered to 25 males with varying degrees of infertility. In the dosage employed, the compound failed to stimulate any definite increase in sperm production. A questionable improvement in sperm motility was observed in a small percentage of the patients treated.—*J.M.*

VAN BRUGGEN, J. T.: A comparison of methods used for the hydrolysis of conjugated urinary estrogens, *J. Lab. & Clin. Med.* **33**: 207–215, 1948.

Several experiments were carried out in order to investigate the various factors which affect the hydrolysis and extraction of conjugated urinary estrogens. Results confirmed previous suggestions that the use of 15 volumes per cent HCl for 10 minutes as the hydrolyzing medium does not give optimum yields of the conjugated estrogens. Nitrogen and sulfonic acid, in contrast to their effectiveness in experiments with pure estrogens, apparently offered little advantage with the combined forms. Two-hour pressure hydrolysis at 120° C. of aliquots of pooled urine, all samples first being adjusted to pH 1.0 with HCl or H_2SO_4, proved to be very effective. The hydrolysis of combined forms of estrogens in butanol gave the highest yields (148,000 units in the 2-hour fraction). Use of a pooled sample of urine appeared to nullify individual differences in urine samples.—*T.H.Mc.G.*

VOGEL, M.; MCGAVACK, T. H., and MELLOW, J.: Effects of various estrogenic preparations on the vaginal mucosa, *Am. J. Obst. & Gynec.* **56**: 269–280, 1948.

Fifty-five postmenopausal patients, ranging in age from 27 to 85 years, were studied. Vaginal smears were obtained prior to therapy, and at 12-hour intervals following administration of a single dose. Periods of observation ranged from 60 to 377 hours. The smears were stained by the Papanicolaou technique. Free estradiol, estradiol dipropionate, estradiol benzoate in sesame oil, peanut oil and propylene glycol, were injected in 1 to 5 milligram amounts. The response noted was as follows: 3 patients, no response; 24 patients, an alteration in type of smear without follicular reaction; and 44 patients, varying degrees of follicular response. The authors found that the degree of follicular reaction and amount of hormone injected could be directly correlated, that an inverse relation existed between age of patient and height of follicular reaction, and that the lag-time between treatment and appearance of the follicular reaction was 42 to 180 hours. The duration of follicular reaction varied from 12 to 200 plus hours, and, in general, the higher doses tended to produce the longer changes. Esters of estradiol in oily menstrua act more rapidly than either free estradiol or its esters, in propylene glycol. It is stressed that there is considerable individual variation in reaction to estrogens, and that doses of estrogen necessary for relief of climacteric symptoms are not quantitatively related to those required to produce a full estrogenic response in the vaginal epithelium.—*C.D.D.*